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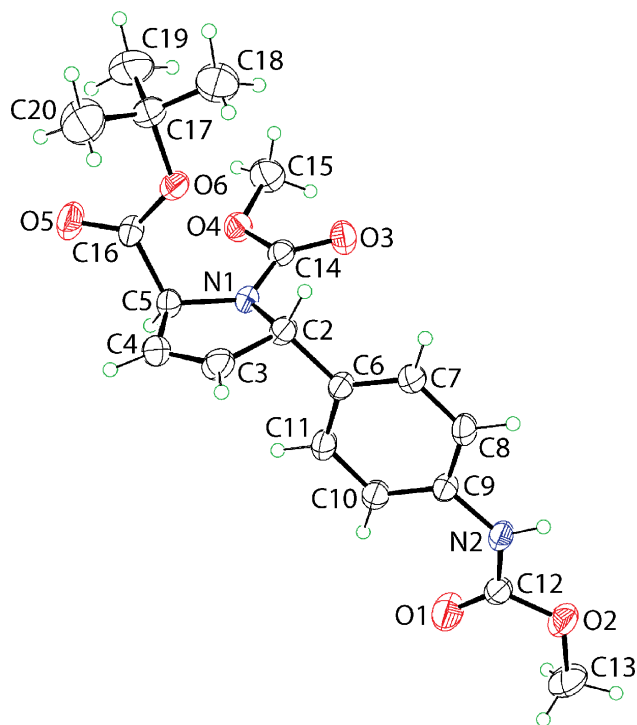
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Crystal structure of 2-*tert*-butyl 1-methyl 5-{4-[(methoxycarbonyl)amino]phenyl}-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, C₁₉H₂₄N₂O₆



Abstract

C₁₉H₂₄N₂O₆, monoclinic, $P2_1$ (no. 4), $a = 8.3611(7)$ Å, $b = 9.0521(8)$ Å, $c = 13.8988(8)$ Å, $\beta = 106.710(5)^\circ$, $V = 1007.52(14)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0428$, $wR_{\text{ref}}(F^2) = 0.1174$, $T = 293(2)$ K.

CCDC no.: 2014879

The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless irregular
Size:	0.40 × 0.32 × 0.30 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.09 mm ⁻¹
Diffractometer, scan mode:	Enraf Nonius TurboCAD4, ω
θ_{max} , completeness:	30.0°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	3294, 3105, 0.025
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 1902
$N(\text{param})_{\text{refined}}$:	252
Programs:	Absorption correction [1], CAD4 [2, 3], SIR2014 [3], SHELX [4], WinGX/ORTEP [5, 6]

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Source of material

To a solution of 2-*tert*-butyl 1-methyl (2*S*)-2,3-dihydro-1*H*-pyrrole-1,2-dicarboxylate (91 mg, 0.40 mol) in dry acetonitrile (2.5 mL), under an inert atmosphere, were added quickly and consecutively anhydrous NaOAc (98 mg, 1.195 mmol), [4-MeOCONHC₆H₄N₂]BF₄ (106 mg, 0.40 mmol, M.pt = 415–416 K; recrystallised from acetone/ether) and Pd₂(dba)₃.dba (5.0 mg, 0.0043 mmol; dba = dibenzylideneacetone). The mixture was stirred at room temperature for 45 min; the progress of the reaction was followed by the release of nitrogen. Then, EtOAc (5.0 mL) and a saturated solution (3.0 mL) of NaHCO₃ were added. The mixture was stirred for 5 min and the phases were separated. The organic phase was washed with water and then with a saturated solution of

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
O1	0.8580(3)	0.2321(3)	0.83858(15)	0.0741(7)
O2	0.9732(2)	0.1773(3)	1.00129(15)	0.0619(6)
O3	0.2235(2)	0.8167(2)	0.82843(12)	0.0528(5)
O4	0.1395(2)	0.9078(2)	0.67070(12)	0.0467(4)
O5	−0.2428(3)	0.7926(3)	0.49100(13)	0.0712(7)
O6	−0.2030(2)	0.7842(2)	0.65798(12)	0.0506(5)
N1	0.1019(2)	0.6687(2)	0.69561(14)	0.0383(5)
N2	0.7240(3)	0.2746(3)	0.95713(15)	0.0472(5)
H2N	0.744(4)	0.268(4)	1.0207(8)	0.057*
C2	0.0947(3)	0.5385(3)	0.75698(18)	0.0424(6)
H2	0.038132	0.564133	0.807465	0.051*
C3	−0.0151(3)	0.4382(3)	0.6794(2)	0.0525(7)
H3	−0.043306	0.342534	0.692777	0.063*
C4	−0.0667(3)	0.5012(3)	0.5903(2)	0.0526(7)
H4	−0.130411	0.453836	0.532597	0.063*
C5	−0.0102(3)	0.6580(3)	0.59370(17)	0.0432(6)
H5	0.049966	0.675981	0.543850	0.052*
C6	0.2642(3)	0.4717(3)	0.80829(17)	0.0401(6)
C7	0.3145(3)	0.4508(3)	0.91076(19)	0.0507(7)
H7	0.244804	0.480145	0.948715	0.061*
C8	0.4675(4)	0.3866(4)	0.95817(18)	0.0521(7)
H8	0.499965	0.374117	1.027515	0.062*
C9	0.5718(3)	0.3411(3)	0.90275(17)	0.0410(6)
C10	0.5229(3)	0.3608(3)	0.79963(18)	0.0478(6)
H10	0.592410	0.331157	0.761632	0.057*
C11	0.3689(3)	0.4252(3)	0.75330(18)	0.0488(7)
H11	0.335716	0.437174	0.683917	0.059*
C12	0.8510(3)	0.2300(3)	0.92356(19)	0.0442(6)
C13	1.1159(4)	0.1162(5)	0.9779(3)	0.0795(11)
H13A	1.157505	0.186115	0.938982	0.119*
H13B	1.084193	0.026899	0.939908	0.119*
H13C	1.201381	0.094735	1.038989	0.119*
C14	0.1593(3)	0.7982(3)	0.73947(17)	0.0402(5)
C15	0.1852(5)	1.0529(4)	0.7103(2)	0.0657(9)
H15A	0.294475	1.049917	0.757550	0.099*
H15B	0.105933	1.086856	0.743443	0.099*
H15C	0.185825	1.119081	0.656452	0.099*
C16	−0.1659(3)	0.7561(3)	0.57373(17)	0.0445(6)
C17	−0.3580(4)	0.8624(4)	0.6599(2)	0.0630(8)
C18	−0.3480(6)	0.8569(7)	0.7699(3)	0.1032(16)
H18A	−0.243749	0.898392	0.808747	0.155*
H18B	−0.355352	0.756109	0.789784	0.155*
H18C	−0.438546	0.912611	0.781328	0.155*
C19	−0.3512(7)	1.0175(5)	0.6252(4)	0.1066(16)
H19A	−0.352571	1.017469	0.555906	0.160*
H19B	−0.250620	1.063784	0.664983	0.160*
H19C	−0.446195	1.071129	0.632398	0.160*
C20	−0.5075(4)	0.7776(7)	0.5956(3)	0.1069(16)
H20A	−0.495320	0.674701	0.612835	0.160*
H20B	−0.514028	0.789744	0.525981	0.160*
H20C	−0.607720	0.814841	0.607453	0.160*

NaCl. The solution was then dried with anhydrous Na₂SO₄, filtered and the solvent was removed in a rotary evaporator. The residue was purified by filtration through a layer of silica gel, using a mixture of EtOAc/*n*-hexane (2:8) as the eluent.

Yield: 148 mg (98%) of Heck products. The products were not separable by flash column chromatography on silica gel, produced a single “spot” by thin layer chromatography and a single signal by capillary gas chromatography. Therefore, the product was dissolved in DMSO and allowed to crystallize slowly. The *trans* diastereoisomer, (I), precipitated; the *cis* diastereoisomer remained in solution.

Suitable crystals for the X-ray diffraction analysis were obtained by slow evaporation from a MeOH solution. **M. pt:** 453–456 K.

The ¹H and ¹³C NMR spectra reflect the presence of conformational rotamers in solution. **¹H NMR** (300 MHz, DMSO-*d*₆ r.t.): δ = 9.62 and 9.61 (2 br s, 1H); 7.39 (d, *J* = 8.1 Hz, 1H); 7.37 (d, *J* = 8.4 Hz, 1H); 7.15 (d, *J* = 8.4 Hz, 1H); 7.13 (d, *J* = 8.4 Hz, 1H); 5.95 and 5.93 and 5.91 [(t, *J* = 1.9 Hz) + (t, *J* = 1.9 Hz) + (t, *J* = 1.6 Hz), 1H]; 5.88 and 5.86 (2q, *J* = 2.2 Hz, 1H); 5.53–5.44 (m, 1H); 5.07 and 5.05 [(t, *J* = 2.2 or 1.6 Hz) + (t, *J* = 1.9 Hz), 1H]; 3.65 (s, 3H); 3.48 and 3.39 (2s, 3H); 1.422 and 1.415 (2s, 9H). **¹H NMR** (300 MHz, DMSO-*d*₆, T = 393 K): δ = 9.05 (br s, 1H); 7.39 (d, *J* = 8.4 Hz, 2H); 7.14 (d, *J* = 8.4 Hz, 2H); 5.93 and 5.91 (2t, *J* = 2.2 or 1.5 Hz, 1H); 5.86 and 5.84 (2t, *J* = 2.2 or 1.8 Hz, 1H); 5.55–5.48 (m, 1H); 5.05 and 5.03 (2t, *J* = 2.2 or 1.8 Hz, 1H); 3.68 (s, 3H); 3.49 (s, 3H); 1.46 (s, 9H). **¹³C NMR** (75 MHz, DMSO-*d*₆, T = 393 K): δ = 167.9; 153.4; 137.6; 134.2; 133.4; 126.2; 122.8; 118.1; 80.5; 67.4; 67.2; 51.0; 50.6; 27.0. **HRMS** (Electron Impact Ionisation) calculated for C₁₉H₂₄N₂O₆: 376.16344; found: 376.16320.

Experimental details

The C-bound H atoms were geometrically placed (C–H = 0.93–0.98 Å) and refined as riding with *U*_{iso}(H) = 1.2–1.5*U*_{eq}(C). The N-bound H atom was refined with N–H = 0.86 ± 0.01 Å, and with 1.2*U*_{eq}(N). The absolute structure was not determined in the X-ray experiment but, the assignment of stereochemistry at the chiral centres is based on the chirality of the synthetic precursor employed in the synthesis.

Comment

Recent reports have detailed the crystal structure determinations of pyrrole [7] and pyrrolidine [8, 9] derivatives having rare or even unprecedented substitution patterns. These are crucial intermediates for the synthesis of pharmacologically-relevant molecules *via* Heck-Matsuda arylation reactions, namely the coupling of an olefin with an arenediazonium salt mediated by a catalytic palladium complex [10]. In the present case, the title compound, (I), is an intermediate in the enantioselective synthesis of polyhydroxylated pyrrolidines such as analogues of Schramm’s antiprotozoan

C-azanucleoside [11], which may display anti-viral, anti-cancer and anti-microbial activities [12, 13]. Herein, the crystal and molecular structures of (I) are described along with an additional analysis of the molecular packing *via* calculated Hirshfeld surfaces.

The molecular structure of (I) is illustrated in the figure (35% displacement ellipsoids) and features a five-membered ring which is twisted about the N1–C5 bond. The geometry about the N1 atom is close to trigonal with the sum of the angles subtended at N1 = 356.2°. The ring is tri-substituted, with a N1-bound methyloxycarbonyl group flanked on either side by a C2-bound [(methoxycarbonyl)amino]phenyl substituent and a C5-bound *tert*-butyloxycarbonyl group. The configuration at each of the C2 and C5 atoms is *S*. The dihedral angle between the N1-substituent and the best plane through the pyrrole ring is 14.91(14)°, being indicative of a twist between the residues. As indicated above, the C2- and C5-bound substituents lie to the opposite side of the pyrrole ring. In fact, they have approximately orthogonal dispositions to the pyrrole ring, forming dihedral angles of 87.83(9) and 83.42(13)°, respectively, with the former. The [(methoxycarbonyl)amino]phenyl is close to planar with the C₆/C₂NO₂ dihedral angle being 2.97(15)°.

There is a single, direct literature precedent for pyrrole (I) which has only been recently described [7]. Here, the N1 atom carries a *tert*-butyloxycarbonyl group and is flanked by C-bound methylhydroxyl and [(methoxycarbonyl)amino]phenyl groups.

In the crystal, amide-N–H···O(carbonyl) hydrogen bonding [N2–H2n···O3ⁱ: H2n···O3ⁱ = 2.083(14) Å, N2n···O3ⁱ = 2.910(3) Å with angle at H2n = 163(3)° for symmetry operation (i): 1 – x, –1/2 + y, 2 – z] connect molecules into a helical supramolecular chain along the b-axis. The presence of methine-C–H···O(amide) [C3–H3···O1ⁱⁱ: H3···O1ⁱⁱ = 2.60 Å, C3···O1ⁱⁱ = 3.294(4) Å with angle at H3 = 132° for (ii) –1 + x, y, z] interactions link the chains into a supramolecular layer in the ab-plane. The layers stack without directional interactions between them. In order to understand more fully the nature of the intermolecular contacts in the crystal, an analysis of the Hirshfeld surfaces along with two-dimensional fingerprint plots was undertaken with the aid of Crystal Explorer 17 [14] and literature protocols [15].

The fingerprint plot delineated into H···O/O···H contacts showed the distinctive spikes due to the N–H···O hydrogen bonds and overall, contributed 24.5% of all contacts, with H···H contacts being most dominant, at 57.9%. The next most significant contribution to the calculated surface contacts is from H···C/C···H contacts [11.6%] with smaller contributions from N···C/C···N [2.9%] and H···N/N···H [2.7%] contacts.

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