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Crystal structure of 2-ethyl-1-*tert*-butyl 3-oxo-2-[phenyl(*tert*-butoxycarbonylamino)methyl]-1,2-pyrrolidinedicarboxylate, $C_{24}H_{34}N_2O_7$

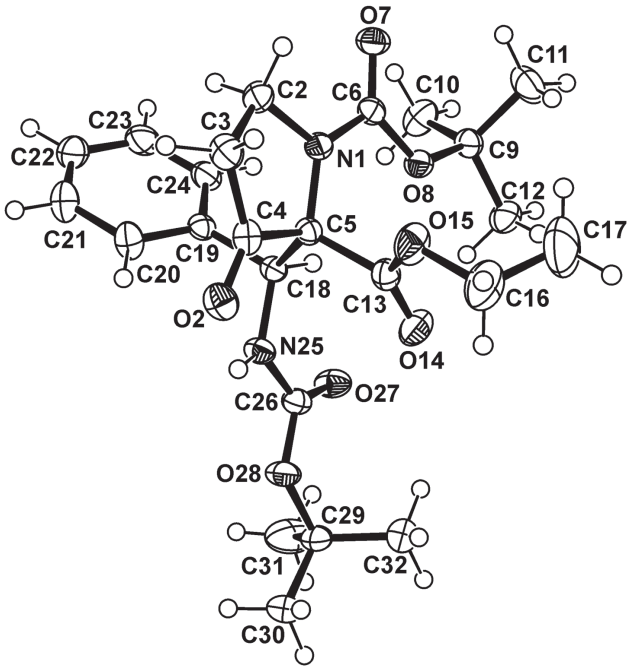

Figure 1: The ORTEP diagram of the asymmetric unit of crystal structure of title compund, $C_{24}H_{34}N_2O_7$.

DOI 10.1515/ncrs-2015-0249
Received October 29, 2015; accepted February 29, 2016; available online March 23, 2016

Abstract

$C_{24}H_{34}N_2O_7$, triclinic, $P\bar{1}$ (no. 2), $a = 9.9562(8)$ Å, $b = 10.7465(9)$ Å, $c = 13.7925(11)$ Å, $\alpha = 95.143°$, $\beta = 109.970(3)°$, $\gamma = 112.229(4)°$, $V = 1242.62(18)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0460$, $wR_{ref}(F^2) = 0.1337$, $T = 173$ K.

CCDC no.: 1456601

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Table 1: Data collection and handling.

Crystal:	Colourless, block, size 0.18×0.24×0.32 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.91 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω scans
$2\theta_{max}$:	57.1°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	22730, 6107
$N(param)_{refined}$:	309
Programs:	Bruker programs [5], SHELX [6], WinGx [7], Mercury [8]

The asymmetric unit of the crystal structure is shown in Figure 1. Tables 1–3 contain details of the measurement method and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

A mixture of 3-keto proline (1.0 eq) and *N*-Boc-aldimines (1.2 eq) was stirred in the presence of proline as catalyst (0.20 eq) at 20°C. The reaction progress was monitored using TLC, the solvent was removed under reduced pressure and the crude product was purified by column chromatography. (ethyl acetate/hexane, 15:85, $Rf = 0.3$) to afford the product (65%) as a yellowish oil. $[\alpha]^{23}_D = +20$ ($c = 0.01$ in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 3H), 7.11–7.04 (m, 2H), 6.63–6.26 (m, 1H), 5.74–5.56 (m, 1H), 4.30–4.03 (m, 2H); 3.92–3.69 (m, 1H), 3.62–3.44 (m, 1H), 2.64–2.58 (m, 1H), 2.54–2.45 (m, 1H), 1.49–1.33 (m, 18H), 1.22–1.16 (m, 3H). The title compound (3.0 mg) was dissolved in acetonitrile (CH_3CN) in a NMR tube by sonication for 3 min. The tube was covered with parafilm with a tiny outlet to enable the solvent to slowly evaporate at ambient conditions. Crystals suitable for X-ray diffraction formed over the period of 15 days.

Experimental details

Data reduction and cell refinement were performed using the program SAINT-Plus [5]. In the case of triclinic crystal system finding the space group is no sorcery. The structure was solved

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

Atom	Site	*x*	*y*	*z*	U_{iso}
H(2A)	2*i*	1.2118	0.8794	0.1026	0.035
H(2B)	2*i*	1.1062	0.9359	0.0184	0.035
H(3A)	2*i*	0.9264	0.7204	−0.0801	0.040
H(3B)	2*i*	1.0678	0.6780	−0.0242	0.040
H(10A)	2*i*	1.1786	1.0864	0.4377	0.060
H(10B)	2*i*	1.1848	1.2372	0.4635	0.060
H(10C)	2*i*	1.2412	1.1973	0.3746	0.060
H(11B)	2*i*	1.0539	1.2685	0.2500	0.069
H(11A)	2*i*	0.9599	1.2844	0.3204	0.069
H(11C)	2*i*	0.8665	1.1747	0.2066	0.069
H(12A)	2*i*	0.7690	1.0102	0.3136	0.054
H(12B)	2*i*	0.8930	1.1121	0.4284	0.054
H(12C)	2*i*	0.8897	0.9643	0.3944	0.054
H(16A)	2*i*	0.4640	0.6326	0.0117	0.063
H(16B)	2*i*	0.4678	0.6675	−0.0982	0.063
H(17A)	2*i*	0.5473	0.8668	0.0861	0.129
H(17B)	2*i*	0.3872	0.8107	−0.0197	0.129
H(17C)	2*i*	0.5544	0.9032	−0.0226	0.129
H(18)	2*i*	1.0062	0.7813	0.3078	0.026
H(20)	2*i*	1.1115	0.5478	0.1791	0.040
H(21)	2*i*	1.3701	0.5839	0.2098	0.047
H(22)	2*i*	1.5852	0.7854	0.3287	0.047
H(23)	2*i*	1.5404	0.9565	0.4104	0.047
H(24)	2*i*	1.2813	0.9260	0.3740	0.037
H(25)	2*i*	0.861(2)	0.505(2)	0.200(1)	0.034(4)
H(30A)	2*i*	0.4860	0.2072	0.2503	0.071
H(30B)	2*i*	0.4927	0.1796	0.3636	0.071
H(30C)	2*i*	0.6285	0.1797	0.3266	0.071
H(31A)	2*i*	0.8437	0.3659	0.4882	0.089
H(31B)	2*i*	0.7092	0.3565	0.5296	0.089
H(31C)	2*i*	0.8250	0.5029	0.5218	0.089
H(32A)	2*i*	0.6061	0.5463	0.3956	0.080
H(32B)	2*i*	0.4806	0.4102	0.4092	0.080
H(32C)	2*i*	0.4710	0.4249	0.2928	0.080

by direct methods using SHELXS [6] and refined by full-matrix least-squares methods based on F^2 using SHELXL-2014 [6] and using the graphics interface program WinGX [7] and Mercury 3.7 [8] were used to prepare molecular graphics. All hydrogen atoms, except H25, were placed in idealised positions and refined in riding models with U_{iso} assigned the values to be 1.2 or 1.5 times those of their parent atoms and the constraint distances of C—H ranging from 0.95 Å to 1.00 Å. The hydrogen atom H25 was located in the difference electron density maps and refined independently.

Discussion

The usefulness of proline to induce turns in peptides can have a significant effect on its biological conformation thereby influencing ligand binding and overall protein activity [1, 2]. The fact that small peptide drugs still have some unresolved issues; researchers have examined proline analogues that

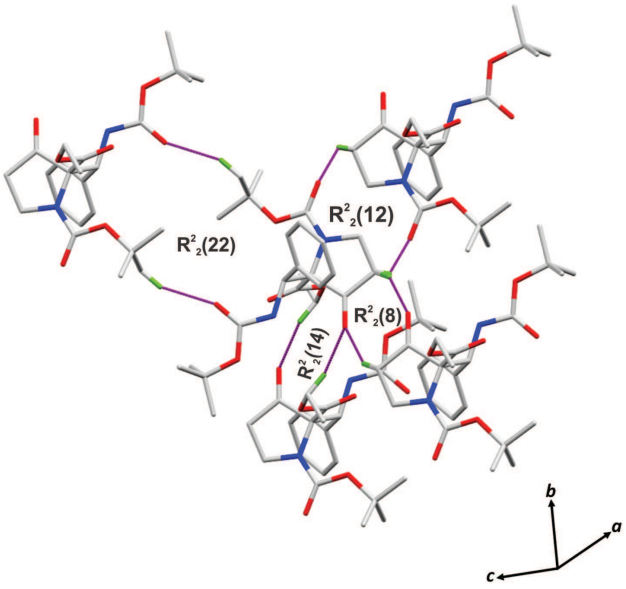

Figure 2: Analysis of the hydrogen bonding scheme of the title structure.

mimic its properties. In addition, unnatural prolines have been employed as organocatalysts [3]. Hence, the asymmetric synthesis of pyrrolidine derivatives for both biological and catalytic purposes has received significant attention. The catalytic asymmetric synthesis of α,α-disubstituted proline analogues have been rather neglected. Currently, we are interested in the synthesis of α,α-disubstituted proline analogues with the aid of current knowledge on organocatalysed α-substitution on the scarcely studied 3-ketoproline backbone [4].

The crystal structure analysis revealed that the oxopyrrolidine ring was distorted as one of its methyl groups (C2) is leaning towards the aromatic ring forming a C—H$\cdots\pi$ interaction (H$\cdots\pi$ = 3.13 Å). The C2 atom deviated from the plane of the remaining four atoms on the oxopyrrolidine ring by 0.345 Å. The hydrogen bonding analysis is given in Figure 2. The carbonylamino group of tert-butoxycarbonylamino lies parallel to the plane of the oxopyrrolidine ring and it is noteworthy that the amino group, a potential hydrogen bond donor, did not form hydrogen bonds with the neighbouring molecule within the crystal. This was perhaps due to a bulky tert-butyloxy substitution attached next to the carbonylamino group. However, C—H$\cdots$O interactions play a pivotal role in stabilizing the molecules in the crystal. Thus the molecules in the crystals are interconnected through four major types of cyclic C—H$\cdots$O hydrogen bond dimers such as; (i) formed between the oxopyrrolidine rings of adjacent molecules [H$\cdots$A = 2.59 Å, D$\cdots$A = 3.5002(3) Å, D—H$\cdots$A = 154°] with the graph set of $R^2_2(8)$ [9], (ii) formed between oxopyrrolidinebutoxycarbonyl moieties [H$\cdots$A = 2.54 Å, D$\cdots$A = 3.3613 (3) Å, D—H$\cdots$A = 140°] with the graph

Table 3: Fractional coordinates and atomic displacement parameters (Å^2).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	2*i*	1.0211(1)	0.8753(1)	0.13056(8)	0.0277(5)	0.0248(5)	0.0242(5)	0.0130(4)	0.0141(4)	0.0093(4)
O(2)	2*i*	0.8377(1)	0.5148(1)	0.02935(8)	0.0355(5)	0.0274(5)	0.0291(5)	0.0123(4)	0.0083(4)	−0.0002(4)
C(2)	2*i*	1.1022(2)	0.8658(2)	0.0607(1)	0.0359(7)	0.0339(7)	0.0286(6)	0.0188(6)	0.0194(6)	0.0118(5)
C(3)	2*i*	1.0004(2)	0.7197(2)	−0.0109(1)	0.0446(8)	0.0347(7)	0.0275(6)	0.0211(6)	0.0191(6)	0.0081(5)
C(4)	2*i*	0.9103(2)	0.6393(1)	0.0481(1)	0.0274(6)	0.0308(7)	0.0204(5)	0.0163(5)	0.0064(5)	0.0032(5)
C(5)	2*i*	0.9223(1)	0.7417(1)	0.14132(9)	0.0236(5)	0.0217(6)	0.0214(5)	0.0105(5)	0.0098(5)	0.0060(4)
C(6)	2*i*	1.0531(2)	1.0023(1)	0.1850(1)	0.0254(6)	0.0256(6)	0.0227(5)	0.0130(5)	0.0097(5)	0.0094(5)
O(7)	2*i*	1.1465(1)	1.1107(1)	0.17901(8)	0.0391(5)	0.0262(5)	0.0361(5)	0.0126(4)	0.0218(4)	0.0118(4)
O(8)	2*i*	0.9654(1)	0.98803(9)	0.24228(7)	0.0302(5)	0.0234(4)	0.0295(4)	0.0112(4)	0.0167(4)	0.0062(4)
C(9)	2*i*	0.9972(2)	1.1081(1)	0.3228(1)	0.0347(7)	0.0245(6)	0.0301(6)	0.0142(5)	0.0177(6)	0.0056(5)
C(10)	2*i*	1.1654(2)	1.1620(2)	0.4071(1)	0.0339(7)	0.0428(9)	0.0353(7)	0.0118(6)	0.0147(6)	−0.0025(6)
C(11)	2*i*	0.9667(2)	1.2187(2)	0.2703(2)	0.072(1)	0.0386(9)	0.0515(9)	0.0363(9)	0.0351(9)	0.0191(7)
C(12)	2*i*	0.8765(2)	1.0429(2)	0.3689(1)	0.0384(7)	0.0371(8)	0.0402(8)	0.0169(6)	0.0244(6)	0.0087(6)
C(13)	2*i*	0.7515(2)	0.7219(1)	0.1185(1)	0.0243(6)	0.0257(6)	0.0288(6)	0.0116(5)	0.0084(5)	0.0045(5)
O(14)	2*i*	0.6859(1)	0.6931(1)	0.17685(9)	0.0295(5)	0.0502(7)	0.0421(6)	0.0189(5)	0.0189(5)	0.0157(5)
O(15)	2*i*	0.6862(1)	0.7347(1)	0.01981(9)	0.0310(5)	0.0589(7)	0.0363(5)	0.0252(5)	0.0095(4)	0.0178(5)
C(16)	2*i*	0.5183(2)	0.7043(2)	−0.0198(2)	0.0307(8)	0.071(1)	0.0485(9)	0.0261(8)	0.0034(7)	0.0142(9)
C(17)	2*i*	0.5002(3)	0.8321(3)	0.0084(3)	0.057(1)	0.085(2)	0.124(2)	0.052(1)	0.023(1)	0.030(2)
C(18)	2*i*	1.0002(1)	0.7124(1)	0.25073(9)	0.0245(5)	0.0194(6)	0.0215(5)	0.0093(5)	0.0101(5)	0.0057(4)
C(19)	2*i*	1.1692(2)	0.7339(1)	0.27269(9)	0.0252(6)	0.0238(6)	0.0215(5)	0.0120(5)	0.0090(5)	0.0096(4)
C(20)	2*i*	1.1983(2)	0.6322(2)	0.2253(1)	0.0312(7)	0.0329(7)	0.0318(7)	0.0179(6)	0.0059(6)	0.0013(6)
C(21)	2*i*	1.3524(2)	0.6527(2)	0.2446(1)	0.0390(8)	0.0466(9)	0.0403(8)	0.0288(7)	0.0134(7)	0.0094(7)
C(22)	2*i*	1.4798(2)	0.7725(2)	0.3141(1)	0.0285(7)	0.0437(9)	0.0520(9)	0.0196(6)	0.0161(7)	0.0209(7)
C(23)	2*i*	1.4529(2)	0.8737(2)	0.3624(1)	0.0266(7)	0.0290(7)	0.0515(9)	0.0078(6)	0.0090(6)	0.0120(6)
C(24)	2*i*	1.2983(2)	0.8551(1)	0.3412(1)	0.0289(6)	0.0230(6)	0.0361(7)	0.0106(5)	0.0100(6)	0.0080(5)
N(25)	2*i*	0.9034(1)	0.5751(1)	0.25539(9)	0.0305(5)	0.0190(5)	0.0268(5)	0.0077(4)	0.0129(5)	0.0050(4)
C(26)	2*i*	0.8418(2)	0.5585(1)	0.3298(1)	0.0249(6)	0.0231(6)	0.0263(6)	0.0090(5)	0.0093(5)	0.0090(5)
O(27)	2*i*	0.8786(1)	0.6502(1)	0.40521(8)	0.0396(5)	0.0291(5)	0.0295(5)	0.0073(4)	0.0187(4)	0.0044(4)
O(28)	2*i*	0.7384(1)	0.4243(1)	0.30790(8)	0.0343(5)	0.0225(5)	0.0375(5)	0.0062(4)	0.0184(4)	0.0098(4)
C(29)	2*i*	0.6524(2)	0.3769(2)	0.3758(1)	0.0291(6)	0.0304(7)	0.0446(8)	0.0123(6)	0.0197(6)	0.0196(6)
C(30)	2*i*	0.5564(2)	0.2222(2)	0.3245(2)	0.0410(8)	0.0277(8)	0.080(1)	0.0120(7)	0.0324(9)	0.0209(8)
C(31)	2*i*	0.7677(3)	0.4028(2)	0.4888(2)	0.058(1)	0.065(1)	0.048(1)	0.017(1)	0.0194(9)	0.0365(9)
C(32)	2*i*	0.5429(2)	0.4456(2)	0.3676(2)	0.0425(9)	0.0391(9)	0.093(2)	0.0218(8)	0.037(1)	0.0227(9)

set of $R^2_2(12)$, (iii) formed between ethylester (H) and oxopyrrolidine (O) atom [H···A = 2.63 Å, D···A = 3.38(2) Å, D—H···A = 132°] with the graph set of $R^2_2(14)$ (iv) formed between tert-butoxycarbonyl (O) atom [H···A = 2.47 Å, D···A = 3.3864(3) Å, D—H···A = 155°] with the graph set of $R^2_2(22)$.

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