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Z. Kristallogr. - N. Cryst. Struct. 2024; 239(6): 1109–1111

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Crystal structure of (3-(dimethoxymethyl)-5-methoxy-1*H*-indol-1-yl)(5-fluoro-2-iodophenyl) methanone, $C_{19}H_{17}FINO_4$

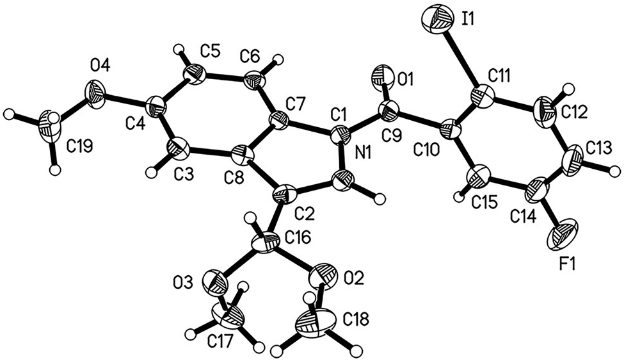

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	$0.15 \times 0.12 \times 0.10$ mm
Wavelength:	Cu *K*α radiation (1.54178 Å)
μ:	$13.8\ \text{mm}^{-1}$
Diffractometer, scan mode:	XtaLAB synergy R, four-circle diffractometer
$\theta_{\max}$, completeness:	74.0°, 97 %
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int}:	9895, 3519, 0.066
Criterion for I_{obs}, $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2\ \sigma(I_{\text{obs}})$, 3042
$N(param)_{\text{refined}}$:	239
Programs:	Rigaku,[1] SHELX[2,3]

https://doi.org/10.1515/ncrs-2024-0321
Received July 29, 2024; accepted September 16, 2024;

Abstract

$C_{19}H_{17}FINO_4$, triclinic, $P\bar{1}$ (no. 2), $a = 7.1158(2)$ Å, $b = 11.1914(3)$ Å, $c = 12.4974(3)$ Å, $\alpha = 73.015(2)°$, $\beta = 87.945(2)°$, $\gamma = 78.137(2)°$, $V = 931.19(4)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0563$, $wR_{ref}(F^2) = 0.1639$, T = 293(2) K.

CCDC no.: 2384291

The crystal structure is shown in figure. Displacement ellipsoids are drawn at the 30 % probability level.

Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

1 Source of material

The target compound (3-(dimethoxymethyl)-5-methoxy-1*H*-indol-1-yl) (5-fluoro-2-iodophenyl)methanone could be synthesized by acylation of 3-(dimethoxymethyl)-5-methoxy-1*H*-indole with corresponding acyl chloride. Firstly, sodium hydride (1.1 g, 27 mmol) and anhydrous *N*,*N*-dimethylformamide (DMF, 12 mL) were added into a 100 mL round bottom flask, and stirred for 5 min in an ice water bath. Secondly, a solution of 3-(dimethoxymethyl)-5-methoxy-1*H*-indole (1.7 g, 7.5 mmol) in anhydrous DMF (10 mL) was added dropwise to the reaction solution, and after the addition was complete, continued stirring for another 5 min. Subsequently, a solution prepared by 5-fluoro-2-iodobenzoyl chloride (3.8 g, 13.5 mmol) and anhydrous DMF (10 mL) was added dropwise. After addition, the reaction mixture was slowly raised to room temperature, and stirred for 4 h. TLC (UV, 254 nm) was used to monitor the reaction process. After the end of reaction, this solution was quenched by saturated ammonium chloride solution carefully, then the crude product precipitated from the mixture. The crude product was homogenized with petroleum ether/ethyl acetate (2:1, *v*/*v*), followed by filtration and washing to obtain pure product (3.0 g, yield 85 %). Single crystals were obtained from the *n*-hexane/ethyl acetate (1:1, *v*/*v*) solution.

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with d (C–H) = 0.96 Å (methyl), $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$, and d(C–H) = 0.98 Å (methyne), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, and d(C–H) = 0.93 Å (aromatic), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

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

Atom	x	y	z	U_{iso}*/U_{eq}
C1	−0.0486 (7)	0.6884 (4)	0.7243 (4)	0.0399 (10)
H1	−0.112865	0.764732	0.675566	0.048*
C2	−0.0532 (6)	0.5729 (4)	0.7163 (4)	0.0368 (9)
C3	0.1171 (7)	0.3466 (4)	0.8385 (4)	0.0416 (10)
H3	0.069593	0.299897	0.799122	0.050*
C4	0.2405 (7)	0.2865 (4)	0.9298 (4)	0.0411 (10)
C5	0.3096 (7)	0.3570 (5)	0.9910 (4)	0.0427 (11)
H5	0.390470	0.314069	1.053136	0.051*
C6	0.2601 (7)	0.4872 (4)	0.9609 (4)	0.0380 (9)
H6	0.306944	0.533507	1.000957	0.046*
C7	0.1381 (6)	0.5475 (4)	0.8690 (4)	0.0335 (9)
C8	0.0660 (7)	0.4793 (4)	0.8071 (3)	0.0354 (9)
C9	0.1071 (7)	0.7797 (4)	0.8472 (4)	0.0429 (10)
C10	0.0311 (7)	0.9098 (4)	0.7680 (4)	0.0419 (10)
C11	0.1382 (8)	0.9640 (5)	0.6785 (5)	0.0480 (11)
C12	0.0715 (11)	1.0861 (5)	0.6101 (5)	0.0633 (16)
H12	0.143458	1.120901	0.549773	0.076*
C13	−0.1002 (12)	1.1564 (5)	0.6307 (7)	0.0726 (19)
H13	−0.145211	1.239528	0.586172	0.087*
C14	−0.2029 (10)	1.1008 (5)	0.7184 (6)	0.0643 (16)
C15	−0.1450 (9)	0.9802 (5)	0.7885 (5)	0.0548 (13)
H15	−0.220139	0.946272	0.847535	0.066*
C16	−0.1543 (7)	0.5433 (5)	0.6271 (4)	0.0433 (10)
H16	−0.055819	0.514220	0.578276	0.052*
C17	−0.4007 (10)	0.4698 (7)	0.7447 (6)	0.0672 (16)
H17A	−0.345003	0.493644	0.802218	0.101*
H17B	−0.449026	0.393511	0.777574	0.101*
H17C	−0.504170	0.537432	0.707337	0.101*
C18	−0.3503 (11)	0.6503 (8)	0.4649 (5)	0.077 (2)
H18A	−0.251511	0.636458	0.412944	0.116*
H18B	−0.440228	0.728164	0.431259	0.116*
H18C	−0.415862	0.580285	0.484269	0.116*
C19	0.2430 (12)	0.0786 (5)	0.9120 (6)	0.0721 (19)
H19A	0.105483	0.091404	0.913661	0.108*
H19B	0.297998	−0.009381	0.948136	0.108*
H19C	0.282640	0.101152	0.835659	0.108*
F1	−0.3745 (7)	1.1691 (4)	0.7407 (5)	0.0983 (15)
I1	0.40179 (6)	0.85710 (4)	0.64563 (4)	0.0756 (3)
N1	0.0660 (6)	0.6790 (4)	0.8160 (3)	0.0373 (8)
O1	0.1957 (7)	0.7661 (4)	0.9313 (4)	0.0613 (11)
O2	−0.2666 (6)	0.6592 (4)	0.5628 (3)	0.0556 (9)
O3	−0.2595 (6)	0.4475 (3)	0.6665 (3)	0.0522 (9)
O4	0.3068 (7)	0.1568 (3)	0.9689 (3)	0.0581 (10)

3 Comment

The research on nitrogen heterocycle compositions has always been a hot topic in organic chemistry and medicinal chemistry.[4] Among the 1086 small molecule drugs approved by the U. S. FDA, 640 drugs (approximately 59 %) contained nitrogen heterocycles in their structures, and indole was the most common fused heterocyclic ring, with 17 new drugs containing this structure, ranking 9th among all heterocycles.[5] In the above context, the synthesis and structural modification of indole skeletons have become significant topics in organic chemistry.[6] The classic strategies for sodium indole synthesis included Bischler–Mohlau (1881),[7] Fischer (1883),[8] Reisset (1897),[9] Nenitzescu (1929)[10] reactions. In addition, Batcho–Leimgruber (1971),[11] Gassman (1974),[12] Hegedus (1976),[13] Mori–Ban (1977),[14] Bartoli (1978),[15] and other named reactions represented new methods in this field. On the other hand, *N*-acylation reactions, Vilsmeier–Haack reactions, Friedel–Crafts reactions, and diverse transition-metal-catalyzed cross-coupling reactions were sodium the most used methods for structure modification of indoles.[16,17] Based on the previous research on the synthesis methodology and activity evaluation of indole derivatives, we designed and synthesized a series of *N*-acyl indole skeletons with methoxy and halogen substituents, which could be utilized as key intermediates for the synthesis of diverse anti-inflammatory or anti-tumor compounds.[18]

Single-crystal structure analysis reveals that there is one molecule in the asymmetric unit (*cf.* the Figure). Bond lengths and angles are within a reasonable range.[19–21] In the title molecule, the halogen substituted benzene ring and indole ring are bridged by a carbonyl group. Due to the conjugation effect between the N(1) atom of indole and the carbonyl group, the bond length of C(9)–N(1) (1.382(6) Å) is significantly shortened compared to normal C–N single bonds, which is similar to C(1)–N(1) (1.397(6) Å) and C(7)–N(1) (1.419(6) Å) of the indole ring. The torsion angles of O(1)–C(9)–N(1)–C(1) and O(1)–C(9)–N(1)–C(7) are 174.7(5)° and −7.6(8)°, respectively, indicating that the amide moiety and indole ring are nearly coplanar. The above phenomenon may be due to conjugation effects and smaller steric hindrance. On the contrary, the torsion angles of O(1)–C(9)–C(10)–C(11) and O(1)–C(9)–C(10)–C(15) are 91.9(7)° and −84.4(7)°, respectively, indicating that the carbonyl group and the benzene ring are almost in a vertical conformation, which may be caused by steric hindrance between the carbonyl oxygen atom and the iodine atom. In summary, due to the above two effects, the indole and the halogen substituted benzene ring are nearly perpendicular, with a dihedral angle of 87.85(2)°. Geometric parameters are all in the expected ranges.[22]

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: National Science Foundation of China (No. 21702018), a Key Research and Development Program of Shandong Province (No. 2019GSF108031).

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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