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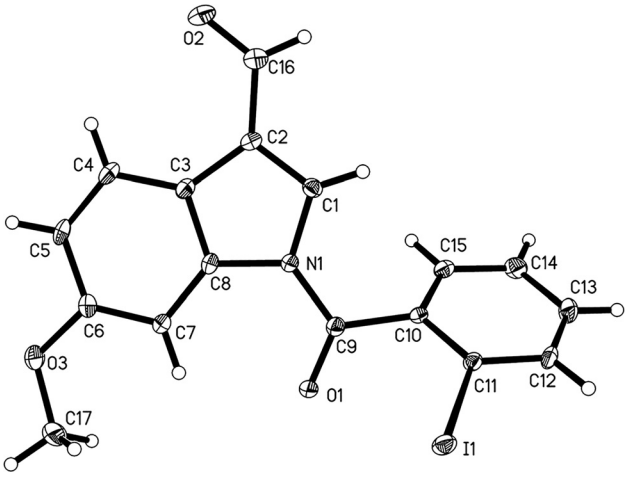
Crystal structure of 1-(2-iodobenzoyl)-6-methoxy-1*H*-indole-3-carbaldehyde, $C_{17}H_{12}INO_3$



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Abstract

$C_{17}H_{12}INO_3$, monoclinic, $P2_1/n$ (no. 14), a = 7.5319(5) Å, b = 7.9745(5) Å, c = 25.1313(17) Å, β = 98.459(7)°, V = 1493.04(17) Å^3, Z = 4, $R_{gt}(F)$ = 0.0272, $wR_{ref}(F^2)$ = 0.0595, T = 199.98(10) K.

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The crystal structure is shown in the figure. Displacement ellipsoids are drawn at the 50% probability level. 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 block
Size:	0.15 × 0.12 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	2.16 mm^{-1}
Diffractometer, scan mode:	SuperNova
θ_{max}, completeness:	25.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	6746, 2777, 0.020
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 2585
$N(param)_{refined}$:	201
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

Source of material

The target compound 1-(2-iodobenzoyl)-6-methoxy-1*H*-indole-3-carbaldehyde could be prepared by acylation of 6-methoxy-1*H*-indole-3-formaldehyde with corresponding acyl chloride. First, sodium hydride (2.2 g, 54 mmol) and anhydrous *N*,*N*-dimethylformamide (DMF, 4 mL) were added into a 250 mL round bottom flask, and stirred in an ice water bath for 5 min. Second, a solution of 6-methoxy-1*H*-indole-3-formaldehyde (2.63 g, 15 mmol) in anhydrous DMF (20 mL) was added dropwise into the above reaction solution, and continued stirring for another 15 min. Next, a solution prepared by 2-iodobenzoyl chloride (7.2 g, 27 mmol) and anhydrous DMF (15 mL) was added dropwise. After addition, the reaction solution was slowly raised to room temperature and stirred for 3 h. The reaction process was monitored by TLC (UV, 254 nm). The crude product was purified by column chromatography (silica gel), eluting with petroleum ether/ethyl acetate (6:1, *v*/*v*) to obtain the white solid product (5.40 g, yield 89%). Single crystals were obtained from *n*-hexane/ethyl acetate (2:1, *v*/*v*) solution.

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_{iso}(H) = 1.5U_{eq}(C), and d(C–H) = 0.93 Å (aromatic), U_{iso}(H) = 1.2U_{eq}(C).

Comment

Indole is a kind of common skeleton exists widely in natural products and drugs, and has been researched in both organic chemistry and medicinal chemistry fields [4]. Especially in the

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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	0.6171 (4)	1.0114 (4)	0.30898 (13)	0.0206 (7)
H1	0.556635	1.052112	0.276628	0.025*
C2	0.5609 (4)	1.0287 (4)	0.35744 (12)	0.0216 (7)
C3	0.6926 (4)	0.9489 (4)	0.39716 (12)	0.0216 (7)
C4	0.7062 (5)	0.9248 (5)	0.45266 (13)	0.0317 (8)
H4	0.617624	0.964856	0.471527	0.038*
C5	0.8520 (5)	0.8415 (5)	0.47869 (14)	0.0370 (9)
H5	0.860964	0.822444	0.515492	0.044*
C6	0.9879 (5)	0.7844 (5)	0.45091 (13)	0.0313 (8)
C7	0.9796 (4)	0.8051 (4)	0.39615 (12)	0.0239 (7)
H7	1.069956	0.766675	0.377713	0.029*
C8	0.8285 (4)	0.8867 (4)	0.37012 (12)	0.0200 (7)
C9	0.8774 (4)	0.8804 (4)	0.27425 (12)	0.0206 (7)
C10	0.7938 (4)	0.9069 (4)	0.21728 (12)	0.0184 (6)
C11	0.8920 (4)	0.9764 (4)	0.17921 (12)	0.0193 (6)
C12	0.8212 (4)	0.9742 (4)	0.12527 (12)	0.0243 (7)
H12	0.884633	1.023135	0.100233	0.029*
C13	0.6572 (5)	0.9001 (4)	0.10826 (13)	0.0300 (8)
H13	0.612329	0.896521	0.071768	0.036*
C14	0.5597 (4)	0.8316 (4)	0.14503 (14)	0.0283 (8)
H14	0.448992	0.781865	0.133484	0.034*
C15	0.6267 (4)	0.8368 (4)	0.19905 (12)	0.0227 (7)
H15	0.558965	0.792706	0.223811	0.027*
C16	0.3977 (5)	1.1145 (4)	0.36499 (15)	0.0312 (8)
H16	0.327604	1.158108	0.334567	0.037*
C17	1.2770 (6)	0.6561 (7)	0.45765 (17)	0.0598 (14)
H17A	1.241793	0.569183	0.431820	0.090*
H17B	1.370215	0.615077	0.484702	0.090*
H17C	1.320657	0.750869	0.439871	0.090*
I1	1.14312 (3)	1.09116 (3)	0.19947 (2)	0.02547 (10)
N1	0.7786 (3)	0.9238 (3)	0.31463 (10)	0.0193 (6)
O1	1.0241 (3)	0.8170 (3)	0.28483 (9)	0.0348 (6)
O2	0.3447 (4)	1.1343 (4)	0.40779 (11)	0.0503 (8)
O3	1.1267 (4)	0.7053 (4)	0.48213 (10)	0.0481 (7)

field of organic synthesis, many researchers have extensively studied the reaction characteristics of the N(1), C(2) and C(3) positions of indole [5–7]. Among them, the most classic reaction is that after being treated with strong base, the negatively charged nitrogen atom shows high nucleophilic activity, so it is easy to acylate with acyl chloride or other reagents to form amide. Many anti-inflammatory drugs containing *N*-acyl substitution indoles, such as indomethacin, could be synthesized or structurally modified through the above acylation reaction [8]. Therefore, this acylation reaction of indole has important applications in drug synthesis [9]. Based on the previous research on the synthetic methodology of indole derivatives [10], we have designed and synthesized a series of compounds with *N*-acyl indole structures, which are expected to exhibit anti-inflammatory or anti-tumor activities. Recently, a series of *N*-acyl indole compounds with active functional groups such as methoxy, aldehyde and iodide substituents have been synthesized by acylation reaction. In this work, the crystals of 1-(2-iodobenzoyl)-6-methoxy-1*H*-indole-3-carbaldehyde were obtained and its structure is reported here.

Single-crystal structure analysis reveals that there are four molecules in the asymmetric unit. Bond lengths and angles are in the expected ranges [11–13]. In title molecule, the iodobenzene part and indole part are bridged by carbonyl group. Due to the conjugation of amide bond in the molecule, the bond length of C(9)–N(1) (1.387(4) Å), is similar to the C(1)–N(1) bond in the indole ring (1.392(4) Å) and is shortened as compared to the C(8)–N(1) bond (1.421(4) Å). The torsion angle O(1)–C(9)–N(1)–C(8) is −5.9(5)°, which indicate the amide moiety and indole ring are almost coplanar. On the contrary, the amide part and the benzene ring of the side chain are not coplanar, because the torsion angles of O(1)–C(9)–C(10)–C(11) is −46.2(4)°. The dihedral angle between the indole ring and the benzene ring is about 55.5(4)°. In addition, as a key intermediate, the title molecule contains methoxy, aldehyde and iodine substituents, which providing plenty of active reaction sites for further modification.

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References

1. Rigaku O. D. CrysAlis^{PRO}; Rigaku Oxford Diffraction Ltd: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick G. M. A short history of SHELX. *Acta Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Kumari A., Singh R. K. Medicinal chemistry of indole derivatives: current to future therapeutic prospectives. *Bioorg. Chem.* 2019, *89*, 103021.
5. Zhu Y., Zhao J., Luo L., Gao Y., Bao H., Li P., Zhang H. Research progress of indole compounds with potential antidiabetic activity. *Eur. J. Med. Chem.* 2021, *223*, 113665.
6. Shiri M. Indoles in multicomponent processes (MCPs). *Chem. Rev.* 2012, *112*, 3508–3549.
7. Taber D. F., Tirunahari P. K. Indole synthesis: a review and proposed classification. *Tetrahedron* 2011, *67*, 7195–7210.
8. Du T., Wei X., Xu H., Zhang X., Fang R., Yuan Z., Liang Z., Li Y. Chemoselective *N*-acylation of indoles using thioesters as acyl source. *Beilstein J. Org. Chem.* 2022, *18*, 89–94.
9. Naaz F., Neha K., Haider M. R., Shafi S. Indole derivatives (2010–2020) as versatile tubulin inhibitors: synthesis and structure-activity relationships. *Future Med. Chem.* 2021, *13*, 1795–1828.

10. Cong W., Zhao L., Wu X., Xu J., Yao H. Facile construction of pyrrolophenanthridone skeleton via a one-pot intramolecular Heck reaction and oxidation. *Tetrahedron* 2014, *70*, 312–317.
11. Ma Z. Y., Lu W., Guo Y. C., Li Y. J. Crystal structure of 2,2-dichloro-1-(4-chloro-1*H*-indol-1-yl)ethan-1-one, $C_{10}H_6Cl_3NO$. *Z. Kristallogr. N. Cryst. Struct.* 2022, *237*, 593–594.
12. Almutairi M. S., Ghabbour H. A., Attia M. I. Crystal structure of methyl 1*H*-indole-2-carboxylate, $C_{10}H_9NO_2$. *Z. Kristallogr. N. Cryst. Struct.* 2017, *232*, 431–432.
13. Cao W.-B., Xu X.-P., Ji S.-J. Copper-catalyzed sequential C(sp^2)/C(sp^3)-H amination of 2-vinylanilines with *N*-fluorobenzenesulfonimide. *Adv. Synth. Catal.* 2019, *361*, 1771–1776.