Malose J. Mphahlele*

Crystal structure of 1-(5-bromo-2-(4-methoxyphenyl)-1*H*-indol-7-yl)ethan-1-ol, $C_{17}H_{14}BrNO_2$

<https://doi.org/10.1515/ncrs-2018-0363>

Received September 10, 2018; accepted October 10, 2018; available online October 25, 2018

Abstract

$C_{17}H_{14}BrNO_2$, monoclinic, $C2/c$ (no. 15), $a = 31.437(3)$ Å, $b = 5.5224(5)$ Å, $c = 16.6545(16)$ Å, $\beta = 94.703(4)^\circ$, $V = 2881.6(5)$ Å³, $Z = 8$, $R_{gt}(F) = 0.0251$, $wR_{ref}(F^2) = 0.067$, $T = 173(2)$ K.

CCDC no.: 1841580

The asymmetric unit of the title crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound was prepared by heating a mixture of 1-(5-bromo-2-(4-methoxyphenyl)-1*H*-indol-7-yl)ethanone (1.00 g, 2.91 mmol) and $PdCl_2$ (0.10 g, 0.58 mmol) in acetonitrile (50 mL) at 80 °C under argon atmosphere for 3 h. Colourless crystals of the title compound, mp. 140–142 °C were obtained

Table 1: Data collection and handling.

Crystal:	Yellow rods
Size:	$0.32 \times 0.26 \times 0.24$ mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ :	2.86 mm^{-1}
Diffractometer, scan mode:	Bruker D8 Venture Photon CCD, ω
$\theta_{\max}$, completeness:	28.0° , >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	60661, 3469, 0.047
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 3212
$N(\text{param})_{\text{refined}}$:	192
Programs:	Bruker [1], WinGX [2], SHELX [3]

by slow evaporation of ethanol and its analytical data was found to compare favourably with the literature data [4].

Experimental details

Measurements were carried out at the Jan Boeyens Structural Chemistry Laboratory (University of the Witwatersrand). Intensity data were collected at -100 °C on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo $K\alpha$ radiation (50 kV, 30 mA). The collection method involved ω scans of width 0.3° . Data reduction was carried out using the program SAINT+ [4] and absorption corrections were made using the program SADABS [1]. The crystal structure was solved by direct methods [2]. Hydrogen atoms were located from the difference map then positioned

*Corresponding author: Malose J. Mphahlele, Department of Chemistry, College of Science Engineering and Technology, University of South Africa, P.O. Box 392 Pretoria 0003, South Africa, e-mail: mphahmj@unisa.ac.za

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

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
C1	0.06650(4)	0.0477(3)	0.43063(8)	0.0249(3)
C2	0.05912(4)	0.1422(3)	0.35304(8)	0.0281(3)
H2	0.038026	0.071166	0.316259	0.034*
C3	0.08252(5)	0.3401(3)	0.32920(9)	0.0303(3)
C4	0.11325(5)	0.4555(3)	0.37942(10)	0.0303(3)
H4	0.128198	0.592261	0.361585	0.036*
C5	0.12167(4)	0.3638(3)	0.45780(9)	0.0256(3)
C6	0.09848(4)	0.1596(2)	0.48135(8)	0.0228(2)
C7	0.15073(4)	0.4267(3)	0.52519(9)	0.0273(3)
H7	0.17049	0.557193	0.527605	0.033*
C8	0.14489(4)	0.2645(2)	0.58563(8)	0.0234(3)
C9	0.16633(4)	0.2416(2)	0.66674(8)	0.0229(2)
C10	0.19513(4)	0.4188(2)	0.69763(9)	0.0254(3)
H10	0.201328	0.553354	0.664994	0.03*
C11	0.21461(4)	0.4009(3)	0.77473(9)	0.0258(3)
H11	0.234161	0.52219	0.794581	0.031*
C12	0.20572(4)	0.2055(2)	0.82356(8)	0.0235(3)
C13	0.17776(5)	0.0270(3)	0.79416(9)	0.0287(3)
H13	0.17179	−0.107738	0.826889	0.034*
C14	0.15846(5)	0.0465(3)	0.71616(10)	0.0294(3)
H14	0.139378	−0.076842	0.696151	0.035*
C15	0.21729(6)	0.0069(3)	0.95026(10)	0.0393(4)
H15A	0.186562	−0.000437	0.956198	0.059*
H15B	0.232721	0.02896	1.003312	0.059*
H15C	0.226517	−0.144294	0.926215	0.059*
C16	0.04160(4)	−0.1564(3)	0.46011(8)	0.0270(3)
C17	0.00601(5)	−0.2633(3)	0.40541(9)	0.0343(3)
H17A	−0.006849	−0.398818	0.432708	0.051*
H17B	0.017408	−0.321483	0.355882	0.051*
H17C	−0.015706	−0.139246	0.391999	0.051*
N1	0.11311(4)	0.1034(2)	0.55875(7)	0.0234(2)
H1	0.103743	−0.016906	0.587139	0.028*
O1	0.04951(4)	−0.2325(2)	0.52853(6)	0.0359(3)
O2	0.22614(3)	0.20540(19)	0.89941(6)	0.0298(2)
Br1	0.07045(2)	0.45143(4)	0.22176(2)	0.04438(8)

geometrically and allowed to ride on their respective parent atoms. Hydrogen atoms involved in hydrogen bonding were located from the difference map and refined freely. Diagrams and publication material were generated using SHELXTL and PLATON [1].

Comment

Indole scaffold continues to attract attention in medicinal chemistry due to its well-known biological properties. Methods for the syntheses of indole-based compounds have been extensively reviewed in the literature over the years. Examples of conventional methods for the synthesis of indoles include the Fisher synthesis from aryl hydrazones, the Batcho-Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassman synthesis

from *N*-haloanilines or the Madelung cyclisation of *N*-acyl-*o*-toluidines [5, 6]. Non-conventional methods that make use of transition metal-mediated C–C and/or C–N bond formation in the construction of the indole nucleus have also been developed. These include the reductive cyclization of *o*-nitrostyrenes [7], the Larock indole synthesis [8], oxidative coupling of acetanilides and internal alkynes [9], the Willis indole synthesis [10], intramolecular Heck cross-coupling of unsaturated halides and alkenes [11], copper-catalyzed indole synthesis [12], C–N coupling of *gem*-dihalovinylanilines [13], C–N coupling of 2-halophenethylamines [14] and cyclization of 2-alkynylaniline derivatives [15, 16]. We have previously exploited the latter strategy on the 2-alkynylanilines derived from 2-amino-5-bromo-3-iodoacetophenone [1, 17] and 2-amino-5-bromo-3-iodobenzamide [18] with terminal acetylenes to afford the corresponding 2-amino-3-(arylalkynyl)acetophenones and 2-amino-3-(arylalkynyl)benzamides. Palladium chloride (PdCl₂)–mediated *endo-dig* (Csp–N) cyclo-isomerization afforded the corresponding indole-based derivatives. During our investigation on the synthesis of medium-sized heterocycles and molecular hybrids incorporating an indole framework, we were able to obtain single crystals of the title compound by slow evaporation of ethanol.

Single crystal XRD analysis confirmed that the title crystal structure contains one molecule in the asymmetric unit (*cf.* the figure) where the indole and 3-(4-methoxyphenyl) group are essentially co-planar with torsion angle about C(7)–C(8)–C(9)–C(14) = −173.19°. There is an intramolecular hydrogen bond between the carbonyl group and NH, (N(1)–H(1)···O(1), with bond distance and bond angle of 2.24 Å and 116°, respectively. All geometric parameters are in the typical ranges and are in excellent accord with those derived from the analogous oxime [19].

Acknowledgements: The author is grateful to the University of South Africa and the National Research Foundation (NRF, SA) for financial assistance. MM Maluleka is thanked for her contribution in the design and proof reading of the manuscript. The author also thanks Prof A. Lemmerer of the University of the Witwatersrand for X-ray diffraction data using the single-crystal diffractometer purchased through the NRF Equipment Programme (UID: 78572).

References

1. Bruker. APEX-3, SAINT+ Version 6.02 (Includes XPREP and SADABS). Bruker AXS Inc., Madison, WI, USA (2016).
2. Farrugia, L. J.: WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* **3** (2012) 837–838.
3. Sheldrick, G. M.: A short history of SHELX. *Acta Crystallogr. A* **64** (2008) 112–122.

4. Mphahlele, M. J.; Parbhoo, N.: Synthesis, evaluation of cytotoxicity and molecular docking studies of the 7-acetamido substituted 2-aryl-5-bromo-3-trifluoroacetylindoles as potential inhibitors of tubulin polymerization. *Pharmaceuticals* **11** (2018) 59–76.
5. Taber, D. F.; Tirunahari, P. K.: Indole synthesis: a review and proposed classification. *Tetrahedron* **67** (2011) 7195–7210.
6. Humphrey, G. R.; Kuethe, J. T.: Practical methodologies for the synthesis of indoles. *Chem. Rev.* **106** (2006) 2875–2911.
7. Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J.: Aqueous titanium trichloride promoted reductive cyclization of *o*-nitrostyrenes to indoles: development and application to the synthesis of rizatriptan and aspidospermidine. *Angew. Chem. Int. Ed.* **127** (2015) 11975–11978.
8. Batail, N.; Bendjeriou, A.; Lomberget, T.; Barret, R.; Dufaud, V.; Djakovitcha, L.: First heterogeneous ligand- and salt-free Larock indole synthesis. *Adv. Synth. Catal.* **351** (2009) 2055–2062.
9. Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K.: Indole synthesis *via* rhodium catalyzed oxidative coupling of acetanilides and internal alkynes. *J. Am. Chem. Soc.* **130** (2008) 16474–16475.
10. Willis, M. C.; Brace, G. N.; Holmes, I. P.: Palladium-catalyzed tandem alkenyl and aryl C–N bond formation: a cascade *N*-annulation route to 1-functionalized indoles. *Angew. Chem. Int. Ed.* **44** (2005) 403–406.
11. Yun, W.; Mohan, R.: Heck reaction on solid support: synthesis of indole analogs. *Tetrahedron Lett.* **37** (1996) 7189–7192.
12. Huang, B.; Hu, D.; Wang, J.; Wan, J.-P.; Liu, Y.: Copper-catalyzed one-pot tandem reactions toward the synthesis of indoles using *o*-iodoanilines, acyl chlorides, and Wittig reagents. *Tetrahedron Lett.* **56** (2015) 2551–2554.
13. Fang, Y.-Q.; Yueng, J.; Lautens, M.: A general modular method of azaindole and thienopyrrole synthesis *via* Pd-catalyzed tandem couplings of *gem*-dichloroolefines. *J. Org. Chem.* **72** (2007) 5152–5160.
14. Monguchi, Y.; Marumoto, T.; Takamatsu, H.; Sawama, Y.; Sajikia, H.: Palladium on carbon-catalyzed one-pot *N*-arylindole synthesis: intramolecular aromatic amination, aromatization, and intermolecular aromatic amination. *Adv. Synth. Catal.* **356** (2014) 1866–1872.
15. Ahmed, A.; Ghosh, M.; Sarkar, P.; Ray, J. K.: ZnCl₂ and Pd/C catalyzed synthesis of 2-substituted indoles. *Tetrahedron Lett.* **54** (2013) 6691–6694.
16. Song, S.; Huang, M.; Li, W.; Zhu, X.; Wan, Y.: Efficient synthesis of indoles from 2-alkynylaniline derivatives in water using a recyclable copper catalyst system. *Tetrahedron* **71** (2015) 451–456.
17. Mphahlele, M. J.; Makhafola, T. J.; Mmonwa, M. M.: *In vitro* cytotoxicity of novel 2,5,7-tricarbo-substituted indoles derived from 2-amino-5-bromo-3-iodoacetophenone. *Bioorg. Med. Chem.* **24** (2016) 4576–4586.
18. Mphahlele, M. J.; Khoza, T. A.; Mabeta, P.: Novel 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinazolin-1-ones: synthesis and biological evaluation. *Molecules* **22** (2017) 55–68.
19. Mphahlele, M. J.: Crystal structure of 1-(5-bromo-2-(4-methoxyphenyl)-1*H*-indol-7-yl)ethanone oxime, C₁₇H₁₅BrN₂O₂. *Z. Kristallogr. NCS* **233** (2018) 889–891.