Jia Gu, Jin-Zhu Chen, Xu-Liang Nie*, Guo-Ping Huang and Jian-Ping Huang*

Crystal structure of 3-chloro-4-(4-ethylpiperazin-1-yl)aniline monohydrate, $C_{12}H_{20}ClN_3O$

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Abstract

$C_{12}H_{20}ClN_3O$, monoclinic, $C2/c$ (no. 15), $a = 27.228(5)$ Å, $b = 11.380(2)$ Å, $c = 9.3775(16)$ Å, $\beta = 95.733(2)^\circ$, $V = 2891.1(9)$ Å³, $Z = 8$, $R_{\text{gt}}(F) = 0.0372$, $wR_{\text{ref}}(F^2) = 0.1058$, $T = 296(2)$ K.

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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.

Source of material

2-Chloro-1-fluoro-4-nitrobenzene (3.52 g, 20 mmol), 1-ethylpiperazine (2.85 g, 25 mmol) and K_2CO_3 (2.76 g,

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	$0.18 \times 0.16 \times 0.13$ mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ :	0.26 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max} , completeness:	25.5° , >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	10,858, 2685, 0.019
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2\sigma(I_{\text{obs}})$, 2149
$N(\text{param})_{\text{refined}}$:	164
Programs:	Bruker [1], SHELX [2, 3], DIAMOND [4]

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

Atom	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.13460 (6)	0.35303 (16)	0.00928 (17)	0.0521 (4)
C2	0.11369 (6)	0.24296 (16)	0.00039 (17)	0.0547 (4)
H2	0.1332	0.1771	0.0228	0.066*
C3	0.06366 (6)	0.22937 (16)	−0.04175 (18)	0.0551 (4)
C4	0.03606 (7)	0.33011 (18)	−0.0733 (2)	0.0614 (5)
H4	0.0026	0.3235	−0.1031	0.074*
C5	0.05739 (7)	0.43980 (17)	−0.06111 (19)	0.0590 (5)
H5	0.0377	0.5056	−0.0818	0.071*
C6	0.10742 (6)	0.45576 (16)	−0.01896 (16)	0.0513 (4)
C7	0.10565 (8)	0.66129 (17)	−0.09501 (19)	0.0648 (5)
H7A	0.0758	0.6833	−0.0534	0.078*
H7B	0.0965	0.6341	−0.1921	0.078*
C8	0.13921 (8)	0.76607 (18)	−0.0976 (2)	0.0692 (5)
H8A	0.1683	0.7444	−0.1432	0.083*
H8B	0.1223	0.8282	−0.1538	0.083*
C9	0.17743 (7)	0.71452 (18)	0.1346 (2)	0.0636 (5)
H9A	0.1857	0.7422	0.2319	0.076*
H9B	0.2078	0.6914	0.0963	0.076*
C10	0.14385 (7)	0.60975 (17)	0.13643 (18)	0.0601 (5)
H10A	0.1602	0.5477	0.1939	0.072*
H10B	0.1141	0.6314	0.1791	0.072*
C11	0.18678 (9)	0.9120 (2)	0.0399 (2)	0.0763 (6)
H11A	0.1711	0.9674	−0.0289	0.092*
H11B	0.2173	0.8864	0.0046	0.092*
C12	0.19886 (9)	0.9741 (2)	0.1803 (3)	0.0877 (7)
H12A	0.1688	0.9953	0.2195	0.132*
H12B	0.2176	1.0438	0.1653	0.132*
H12C	0.2179	0.9230	0.2459	0.132*
N1	0.04314 (6)	0.11767 (14)	−0.06126 (18)	0.0676 (4)
H1A	0.0126	0.1100	−0.0936	0.081*
H1B	0.0610	0.0564	−0.0410	0.081*

*Corresponding authors: Xu-Liang Nie, Department of Chemistry/Key Laboratory of Chemical Utilization of Plant Resources of Nanchang, Jiangxi Agricultural University, Nanchang 330031, People's Republic of China, E-mail: niexuliang1981@163.com. <https://orcid.org/0000-0002-9449-8932>; and Jian-Ping Huang, College of Sciences/Jiangxi Key Laboratory for Conservation and Utilization of Fungal Resources, Jiangxi Agricultural University, Nanchang 330045, People's Republic of China, E-mail: huangchenchuan@126.com. <https://orcid.org/0000-0001-9708-6856>

Jia Gu, College of Sciences, Jiangxi Agricultural University, Nanchang 330045, People's Republic of China

Jin-Zhu Chen, Department of Chemistry/Key Laboratory of Chemical Utilization of Plant Resources of Nanchang, Jiangxi Agricultural University, Nanchang 330031, People's Republic of China

Guo-Ping Huang, Nanchang Jiangteng Pharmaceutical Co., Ltd, Nanchang 330045, People's Republic of China

Table 2: (continued)

Atom	x	y	z	U _{iso} */U _{eq}
N2	0.13080 (6)	0.56732 (13)	−0.01063 (14)	0.0556 (4)
N3	0.15420 (6)	0.80964 (13)	0.04760 (15)	0.0584 (4)
O1	0.06796 (6)	0.91711 (15)	0.13827 (18)	0.0796 (4)
Cl1	0.19832 (2)	0.36051 (5)	0.05142 (6)	0.0784 (2)
H1W	0.0921 (7)	0.8755 (19)	0.125 (2)	0.100 (9)*
H2W	0.0637 (9)	0.918 (2)	0.2244 (12)	0.106 (10)*

20 mmol) were dissolved in dry *N,N*-dimethylformamide (40 mL) with stirring and heating at 90 °C for 1 h [5]. At the beginning of the reaction, the solution was orange and cloudy. After the reaction completed (monitored by TLC), it was naturally cooled to room temperature, water was added to the mixture, and a large amount of brown product was precipitated. The product was filtered, washed with water three times respectively and air-dried. The yield was 99% (based on 2-chloro-1-fluoro-4-nitrobenzene). The above solid and palladium (Pd/C 5%) catalyst were dissolved in the dry methanol at room temperature, and reacted for 2 h under hydrogen pressures [6]. After the reaction is completed (TLC detection), the catalyst was filtered off, and the filtrate was concentrated and dried under reduced pressure. The title compound (1.024 g) was obtained. The yield was 83%. Elemental Anal. Calcd. (%) for C₁₂H₂₀ClN₃O (257.76): C, 60.12; H, 7.57; N, 17.53. Found (%): C, 58.65; H, 7.66; N, 17.10. The crystals of the title compound were obtained from ethyl acetate after one week of slow volatilisation at room temperature.

Experimental details

H atoms were included in calculated positions and refined as riding atoms, with C–H = 0.93 Å with $U_{iso}(H) = 1.5 U_{eq}(C)$ for methyl H atoms and $1.2 U_{eq}(C)$ for all other H atoms.

Comment

Piperazine compounds are an important branch of heterocyclic compounds. Piperazine compounds have important effects on the human body, such as stimulating psychology, causing hallucinations, anti-tumor and anti-cancer [7]. Especially 1,4-disubstituted piperazine derivatives can be used as important intermediates in the synthesis of clinical piperazine APIs, such as Etoperidone, Mepiprazole, Nefazodone (Nefazodone) etc. [8]. Even 1,4-disubstituted piperazine derivatives combined with other groups can be used as drugs for the treatment of Alzheimer's disease [9]. However,

there are hallucinogenic and psychological stimulation effects of piperazine derivatives [5]. After long time use, it will bring many unpredictable problems. Therefore, the synthesis and biological activity of piperazine derivatives have received attention by chemists.

There is one organic molecule and one water molecule in the asymmetric unit (shown in the Figure). In the molecule of the title compound bond lengths and angles within 3-chloro-4-(4-ethylpiperazin-1-yl)aniline are very similar to those given in the literature for butyl 4-((2-chloro-4-(4-hexanoylpiperazin-1-yl) phenyl)diazanyl)benzoate [6] and another closely related molecule [10]. The piperazine ring of the title compound adopts chair conformation. The torsion angles of C1–C6–N2–C7, C6–N2–C7–C8 and C8–N3–C11–C12 are 155.7(2)°, −169.2(2)° and 170.0(2)°, respectively.

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