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Crystal and Molecular Structure of 4-piperidin-1-yl-2-[3-(Trifluoromethyl)phenyl] furo[2,3-c]-pyridine

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Abstract

In the molecular structure of the title compound, $C_{19}H_{17}F_3N_2O$, the furopyridine ring system and the benzene ring are almost coplanar, making a dihedral angle of 5.7 (1)°. In the crystal structure, molecules are linked into adjacent layers parallel to the *bc* plane by intermolecular C—H....N and C—H..F hydrogen bonds, resulting in the formation of a three-dimensional network. The piperidine ring has a chair conformation. The central furopyridine ring is essentially planar, with an r.m.s. deviation of 0,029 (3)Å. The dihedral angle between the furopyridine ring and the mean plane (C11/C12/C14/C15) of the piperidine ring is 42.5 (2)° .

Keywords: crystal and molecular structure, furopyridine, single-crystal X-ray study, trifluoromethyl

Introduction

In recent years, fluorinated compounds have been very important in the pharmaceutical field. Incorporation of an F atom instead of an H atom can alter the course of the reaction as well as biological activities. Introduction of further F atoms in a CF_3 group provides better lipophilicity and the compounds might be pharmacologically more interesting compared to their non-fluorinated analogues.

Many heterocyclic compounds, which bear the trifluoromethyl group, possess a wide range of biological activity (Navarrete-Vazquez et al., 2006), as herbicides (Bravo et al., 1994), fungicides (Jung et al., 2002) and inhibitors for platelet aggregation (Kücükgüzel et al., 2000). 7-(Trifluoromethyl)-quinoline derivatives have been evaluated for *in vitro* activity against some parasites in blood (Abadi and Brun, 2003). Furo[3,2-*c*]pyridine and its derivatives represent isoquinoline isosters, in which the benzene ring is replaced by the furan. The pyridine ring of this system can be readily coordinated to metal centers through N-donor atom. Structural characterization of isothiocyanate nickel(II) complexes with furo[3,2-*c*]pyridine and its 2-methyl, 2,3-dimethyl analogues, and [1]benzofuro[3,2-*c*]pyridine (Bzfupy) have been reported (Miklovič et al., 2004; Baran et al., 2005).

In this study, we have synthesized 4-piperidin-1-yl-2-[3-(trifluoromethyl)phenyl] furo[2,3-c]-pyridine, (Fig.1.), and characterized by X-ray diffraction method.

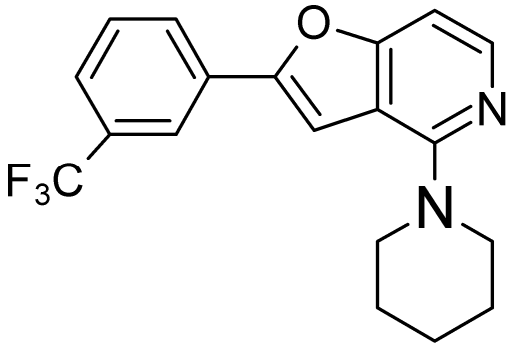

Fig. 1 The molecular structure of the title compound

Experimental

Syntheses of the title compound has been discribed (Bradiaková et al., 2007). In short, 4-piperidin-1-yl-2-[3-(Trifluoromethyl)phenyl]furo[3,2-*c*]pyridine was synthesized by a five steps modified Eloy-Deryckere method starting from 5-[3-(trifluoromethyl)phenyl]furan-2-carbaldehyde. Condensation of this carbaldehyde with malonic acid afforded 3-{5-[3-(trifluoromethyl)phenyl]furan-2-yl}propenoic acid. The obtained acid was converted to the corresponding azide, which was cyclized by heating in diphenyl ether to 2-[3-(trifluoromethyl)phenyl]furo[3,2-c]pyridine-4(5H)-one. This compound was aromatized with phosphorus oxychloride to chloroderivative. Refluxing of 4-chloro-2-[3-(trifluoromethyl)phenyl]furo[3,2-c]pyridine with secondary amine piperidine gave 4-

piperidin-1-yl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*c*]pyridine. Colorless plate-like single crystals suitable for x-ray analysis were prepared by recrystallization from an acetone solution.

Refinement

Refinement of F^2 against all reflections. The weighted *R*-factor *wR* and goodness of fit S are based on F^2, conventional *R*-factors *R* are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on F, and R– factors based on all data will be even larger. All H atoms were placed in geometrically calculated positions and allowed to ride on their parent atoms, with C—H distances of 0.93 Å and U_{iso} set at $1.2U_{eq}$ of the parent atom.

Data collection

CrysAlis CCD (Oxford Diffraction, 2006); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2006); data reduction: *CrysAlis RED* (Oxford Diffraction, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg, 2001); software used to prepare material for publication: *enCIFer* (Allen et al., 2004).

Crystal data and structure refinement

Empirical formula	$C_{19}H_{17}F_3N_2O$
Formula weight	Mr = 346.35
Temperature	298(2) K
Wavelength	λ = 0.71073 Å , Mo K_α radiation,
Crystal system, space group	Monoclinic, $P2_1/c$
Hall symbol	-P 2ybc
Unit cell dimensions	a = 14.4634(7) Å
	b = 9.4448(4) Å
	c = 12.7585(5) Å
	β = 110.771 (5)º
Volume	V = 1629.6 (1) $Å^3$
Z, Calculated density	4, 1.412 Mg/m^3
Absorption coefficient	μ = 0.112 mm^{-1}
F(000)	720
Crystal size	0.31 × 0.17 × 0.02 mm
Theta range for data collection	4.19 to 26.37º

Limiting indices	-18<=h<=18, -11<=k<=11, -15<=l<=15
Reflections collected/unique	58433 / 3312 ;1852 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3312 / 0 / 227
Goodness-of-fit on F^2	S = 1.080
Final R indices [I>2sigma(I)]	R1 = 0.0654, wR2 = 0.2003
Extinction coefficient	0.003(3)
Largest diff. peak and hole	0.471 and -0.334 e.A^{-3}
	$(\Delta/\sigma)_{max}$ < 0.001
Monochromator	graphite

Table 1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3).

atom	x	y	z	U(eq)
C(2)	3447(2)	10455(3)	-1274(2)	62(1)
C(3)	2829(2)	11259(3)	-2107(2)	66(1)
C(5)	1782(2)	11868(3)	-1157(2)	53(1)
C(6)	2487(2)	10865(3)	937(2)	50(1)
C(7)	3291(2)	10057(3)	1416(2)	49(1)
C(8)	3209(2)	10423(3)	-318(2)	51(1)
C(9)	2407(2)	11113(3)	-203(2)	48(1)
C(11)	415(3)	13502(5)	-2094(4)	107(2)
C(12)	-627(3)	13341(6)	-2536(3)	118(2)
C(13)	-1097(3)	13266(5)	-1662(4)	108(1)
C(14)	-544(3)	12218(7)	-775(5)	155(3)
C(15)	471(3)	12352(7)	-374(4)	140(2)
C(16)	3737(2)	9435(3)	2529(2)	49(1)
C(17)	3253(2)	9539(3)	3294(2)	53(1)
C(18)	3654(2)	8930(3)	4342(2)	55(1)
C(19)	4550(2)	8217(3)	4652(2)	61(1)
C(20)	5028(2)	8125(3)	3901(3)	65(1)
C(21)	4629(2)	8718(3)	2845(2)	57(1)
C(22)	3094(2)	9007(4)	5118(2)	67(1)
N(4)	2026(2)	11955(2)	-2081(2)	61(1)
N(10)	927(2)	12511(3)	-1208(2)	72(1)
O(1)	3755(1)	9766(2)	661(1)	55(1)
F(23)	2666(2)	10230(3)	5095(2)	117(1)
F(24)	2405(2)	8021(3)	4890(2)	123(1)
F(25)	3638(2)	8780(3)	6178(1)	103(1)

Table 2 The geometric parameters: bond lengths [Å] and angles [°]

C(2)-C(3)	1.353(4)	C(6)-C(7)-C(16)	133.2(2)
C(2)-C(8)	1.379(4)	O(1)-C(7)-C(16)	116.2(2)
C(3)-N(4)	1.344(4)	O(1)-C(8)-C(2)	125.0(2)
C(5)-N(4)	1.348(3)	O(1)-C(8)-C(9)	110.5(2)
C(5)-N(10)	1.358(4)	C(2)-C(8)-C(9)	124.4(3)
C(5)-C(9)	1.425(4)	C(8)-C(9)-C(5)	116.6(2)
C(6)-C(7)	1.342(4)	C(8)-C(9)-C(6)	105.2(2)
C(6)-C(9)	1.436(3)	C(5)-C(9)-C(6)	138.2(2)
C(7)-O(1)	1.382(3)	C(12)-C(11)-N(10)	114.7(4)
C(7)-C(16)	1.459(4)	C(11)-C(12)-C(13)	114.1(4)
C(8)-O(1)	1.367(3)	C(12)-C(13)-C(14)	109.3(3)
C(8)-C(9)	1.383(4)	C(15)-C(14)-C(13)	115.6(4)
C(11)-C(12)	1.417(6)	C(14)-C(15)-N(10)	116.1(4)
C(11)-N(10)	1.452(4)	C(21)-C(16)-C(17)	118.6(2)
C(12)-C(13)	1.500(5)	C(21)-C(16)-C(7)	121.6(2)
C(13)-C(14)	1.503(6)	C(17)-C(16)-C(7)	119.7(2)
C(14)-C(15)	1.378(6)	C(18)-C(17)-C(16)	120.5(3)
C(15)-N(10)	1.444(4)	C(17)-C(18)-C(19)	120.5(2)
C(16)-C(21)	1.385(4)	C(17)-C(18)-C(22)	119.0(3)
C(16)-C(17)	1.391(4)	C(19)-C(18)-C(22)	120.5(2)
C(17)-C(18)	1.380(4)	C(20)-C(19)-C(18)	118.9(3)
C(18)-C(19)	1.389(4)	C(19)-C(20)-C(21)	121.2(3)
C(18)-C(22)	1.486(4)	C(20)-C(21)-C(16)	120.3(3)
C(19)-C(20)	1.369(4)	F(23)-C(22)-F(25)	105.8(3)
C(20)-C(21)	1.382(4)	F(23)-C(22)-F(24)	107.6(3)
C(22)-F(23)	1.306(4)	F(25)-C(22)-F(24)	104.0(3)
C(22)-F(25)	1.318(3)	F(23)-C(22)-C(18)	113.2(3)
C(22)-F(24)	1.319(4)	F(25)-C(22)-C(18)	114.1(3)
C(3)-C(2)-C(8)	113.9(3)	F(24)-C(22)-C(18)	111.5(3)
N(4)-C(3)-C(2)	126.2(3)	C(3)-N(4)-C(5)	119.2(2)
N(4)-C(5)-N(10)	116.6(2)	C(5)-N(10)-C(15)	124.3(3)
N(4)-C(5)-C(9)	119.6(2)	C(5)-N(10)-C(11)	121.9(2)
N(10)-C(5)-C(9)	123.8(2)	C(15)-N(10)-C(11)	113.6(3)
C(7)-C(6)-C(9)	107.4(2)	C(8)-O(1)-C(7)	106.3(2)
C(6)-C(7)-O(1)	110.6(2)		

Table 3 The geometric parameters: torsion angles [deg]

C(8)-C(2)-C(3)-N(4)	-2.1(5)	C(17)-C(18)-C(19)-C(20)	-0.2(4)
C(9)-C(6)-C(7)-O(1)	0.6(3)	C(22)-C(18)-C(19)-C(20)	177.7(3)
C(9)-C(6)-C(7)-C(16)	-178.2(3)	C(18)-C(19)-C(20)-C(21)	-0.5(5)
C(3)-C(2)-C(8)-O(1)	-175.5(3)	C(19)-C(20)-C(21)-C(16)	0.7(4)
C(3)-C(2)-C(8)-C(9)	1.3(4)	C(17)-C(16)-C(21)-C(20)	-0.2(4)
O(1)-C(8)-C(9)-C(5)	178.9(2)	C(7)-C(16)-C(21)-C(20)	-179.2(3)
C(2)-C(8)-C(9)-C(5)	1.7(4)	C(17)-C(18)-C(22)-F(23)	-40.1(4)
O(1)-C(8)-C(9)-C(6)	0.8(3)	C(19)-C(18)-C(22)-F(23)	141.9(3)
C(2)-C(8)-C(9)-C(6)	-176.3(3)	C(17)-C(18)-C(22)-F(25)	-161.3(3)
N(4)-C(5)-C(9)-C(8)	-4.2(4)	C(19)-C(18)-C(22)-F(25)	20.8(4)
N(10)-C(5)-C(9)-C(8)	174.9(3)	C(17)-C(18)-C(22)-F(24)	81.4(4)
N(4)-C(5)-C(9)-C(6)	172.9(3)	C(19)-C(18)-C(22)-F(24)	-96.5(3)
N(10)-C(5)-C(9)-C(6)	-7.9(5)	C(2)-C(3)-N(4)-C(5)	-0.4(5)
C(7)-C(6)-C(9)-C(8)	-0.9(3)	N(10)-C(5)-N(4)-C(3)	-175.5(3)
C(7)-C(6)-C(9)-C(5)	-178.3(3)	C(9)-C(5)-N(4)-C(3)	3.7(4)
N(10)-C(11)-C(12)-C(13)	49.4(7)	N(4)-C(5)-N(10)-C(15)	170.3(4)
C(11)-C(12)-C(13)-C(14)	-48.5(7)	C(9)-C(5)-N(10)-C(15)	-8.9(5)
C(12)-C(13)-C(14)-C(15)	47.5(7)	N(4)-C(5)-N(10)-C(11)	-13.5(5)
C(13)-C(14)-C(15)-N(10)	-47.0(8)	C(9)-C(5)-N(10)-C(11)	167.3(3)
C(6)-C(7)-C(16)-C(21)	-174.8(3)	C(14)-C(15)-N(10)-C(5)	-139.1(5)
O(1)-C(7)-C(16)-C(21)	6.4(4)	C(14)-C(15)-N(10)-C(11)	44.4(7)
C(6)-C(7)-C(16)-C(17)	6.2(5)	C(12)-C(11)-N(10)-C(5)	137.9(4)
O(1)-C(7)-C(16)-C(17)	-172.6(2)	C(12)-C(11)-N(10)-C(15)	-45.5(6)
C(21)-C(16)-C(17)-C(18)	-0.5(4)	C(2)-C(8)-O(1)-C(7)	176.7(3)
C(7)-C(16)-C(17)-C(18)	178.5(2)	C(9)-C(8)-O(1)-C(7)	-0.5(3)
C(16)-C(17)-C(18)-C(19)	0.7(4)	C(6)-C(7)-O(1)-C(8)	-0.1(3)
C(16)-C(17)-C(18)-C(22)	-177.2(3)	C(16)-C(7)-O(1)-C(8)	178.9(2)

Table 4 Hydrogen bonds [Å and deg.].

D- H A	d(D - H)	d(H.....A)	d(D...A)	<(DHA)
C6 - H N4 [i]	0.93	2.73	3.503 (5)	141
C14 - H14B ...F24[ii]	0.93	2.59	3.355 (7)	136

Symmetry codes: (i) x, 2.5 - y, 0.5 + z; (ii) -x, 0.5 + y, -z + 0.5

Results and Disccusion

The molecular geometry and the atom-numbering scheme of the title compound is shown in Fig.2. The atomic coordinates and equivalent isotropic displacement parameters of (I) are in Table 1, the geometric parameters are in Table 2 and Table 3. The molecule as a whole is nonplanar but consist of approximately planar phenyl-furo-pyridine segment and piperidine ring with dihedral angle 42.5 (2)°. The central furo[3,2-*c*]pyridine ring system is essentially planar, with an r.m.s. deviation of 0.029 Å. The dihedral angle between the furo[3,2-*c*]pyridine ring system and the benzene ring is 5.7 (1)°. The piperidine ring has a chair conformation. In the molecule of (I) (Table 2), the bond lengths and angles are within normal ranges (Allen et al., 1987). The N atom of the furopyridine ring and the F atom of the trifluoromethyl group are involved in intermolecular hydrogen bonding. The intermolecular C6—H6···N4 and C14—H14···F24 interactions link the molecules into layers parallel to the *bc* plane. Neighboring planes of molecules are connected through additional ring stacking interactions [shortest contact is C5···C12 (-*x*, -1/2 + *y*, -1/2 - *z*), 3.599 (5) Å], resulting in a three-dimensional framework structure. Additional hydrogen-bonding parameters are listed in Table 4.

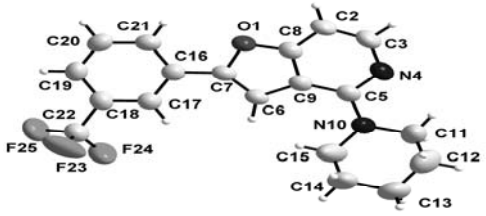

Fig. 2 The molecular structure of the title compound, with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level

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