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1-Fluoromethyl-1-methyl-1*H*,3*H*-thiazolo-[3,4-*a*]benzimidazole

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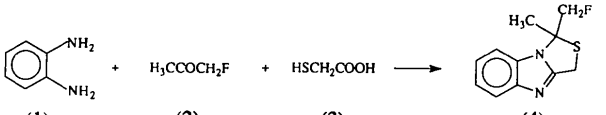
Abstract

The title compound, $C_{11}H_{11}FN_2S$, was obtained by a one-pot synthetic route from 1,2-phenylenediamine, fluoroacetone and 2-mercaptoacetic acid. Both enantiomers are present in the crystal; they are disordered about a crystallographic mirror plane containing the thiazolobenzimidazole system which, for this reason, is perfectly planar.

Comment

In connection with our studies on heteropolycyclic compounds with potential activity against human immunodeficiency virus (HIV) (Chimirri, Grasso, Monforte, Monforte & Zappalá, 1991*a*,*b*; Monforte *et al.*, 1993; Bruno *et al.*, 1996; Chimirri *et al.*, 1996), we report here the synthesis, spectroscopic data and crystal structure of 1-fluoromethyl-1-methyl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole, (4). Our aim was to elucidate further the effects of the C1 substituents on both the stereochemistry and the *anti*-HIV activity of thiazolobenzimidazole derivatives. In fact, some thiazolobenzimidazoles reported previously (Chimirri *et al.*, 1991; Monforte *et al.*, 1993; Bruno *et al.*, 1996; Chimirri *et al.*, 1996), have proved to be potent non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors (Schultz *et al.*, 1992; Buckheit *et al.*, 1993), but only if some structural features necessary for the inhibition of the RT enzyme (Scafer *et al.*, 1993) are present. The synthesis of compound (4) was carried out by reaction of 1,2-phenylenediamine, (1), with fluoroacetone, (2), and 2-mercaptoacetic acid, (3).



(1) (2) (3) (4)

Spectroscopic methods (MS and ^{1}H-NMR) were useful in confirming the proposed structure. In order to study the geometry of the synthesized compound, (4), and in particular the orientation of the substituents at C1, the crystal structure analysis was undertaken. The thiazolobenzimidazole system comprises of a fused three-ring system, a benzimidazole system fused to a thiazole ring. The thiazole ring has a chiral centre in position 1 to which a methyl and a monofluoromethyl group are bonded. From the synthetic process, we obtained a racemic mixture of the title compound. Both enantiomers are present in the crystals; the molecules lie on crystallographic mirror planes with the *R* and *S* isomers alternating, resulting in a disorder of the C1 substituents.

The three fused rings are perfectly planar as required by symmetry. In the thiazole ring, the bond distances S—C1 [1.847 (2) Å] and S—C9 [1.808 (2) Å] are in agreement with those found in analogous compounds (DeTitta, Edmonds, Stallings & Donohue, 1976; In *et al.*, 1990). The significant difference between the two S—C distances is due to the steric effect of the two substituents of the chiral atom [S···C10 = 2.738 (2) Å]; The C1—S—C9 bond angle [96.69 (9)°] has one of the highest values found in the Cambridge Structural Database (Allen *et al.*, 1991) for sulfur-containing five-membered-ring systems similar to that in our compound. In all these molecules, the five-membered ring assumes an envelope conformation; the tendency towards this stereochemical situation accounts for the large value of the U_{22} component of the sulfur displacement parameter. In the benzimidazole ring, there is a wide π-electron delocalization as can be seen by analysing the fragment geometry. This is borne out in the bond distances N2—C2 = 1.387 (2), N2—C8 = 1.360 (2), C8—N1 = 1.304 (2) and C7—N1 = 1.395 (2) Å. The molecular

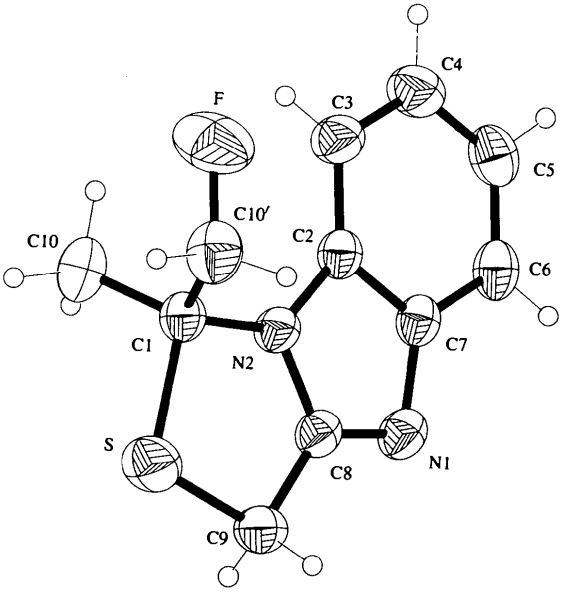


Fig. 1. Plot of the title compound showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level.

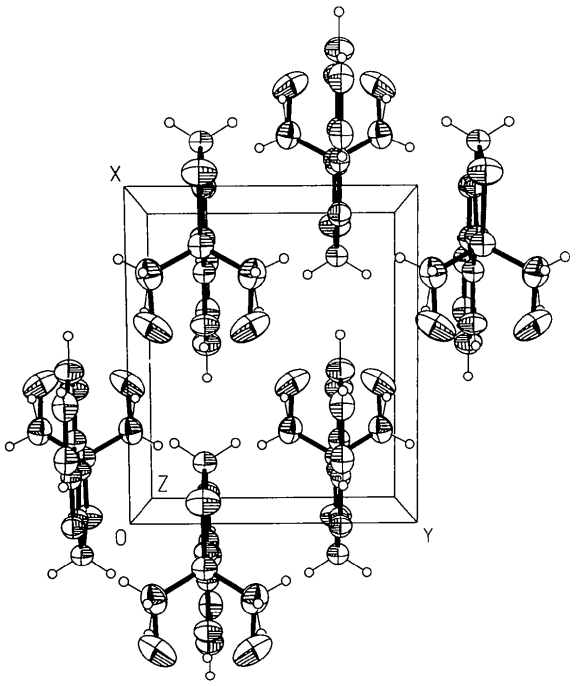


Fig. 2. Molecular packing in the crystal. The two enantiomers are shown as overlapped.

packing, shown in Fig. 2, is essentially determined by normal Van der Waals interactions and by weak hydrogen bonds involving the F and N1 atoms.

Experimental

To a stirred solution of 1,2-phenylenediamine (1) (2.7 g, 0.025 mol) in anhydrous benzene (80 ml), a solution of fluoroacetone (2) (1,9 g, 0.025 mol) in the same solvent (20 ml) was added. The resulting mixture was treated dropwise with an excess of 2-mercaptoacetic acid (3) (4.6 g, 0.13 mol) and heated under reflux for 20 h. The optimum reaction time was determined by TLC monitoring (8:2 ethyl ether/petroleum ether). The solution obtained was washed with 2% $NaHCO_3$ solution until neutral. The solvent was evaporated under reduced pressure and the oily residue was chromatographed on a silica gel column (ethyl ether/petroleum ether 8:2) to afford, after recrystallization from ethanol, compound (4) as yellow platelets. Single crystals of the title compound suitable for X-ray analysis were obtained by slow evaporation of an ethyl ether solution at room temperature. Yield 47.1%; m.p. 353–354 K. MS *m/z* (%): 222 (M^+, 48), 189 (100), 143 (8), 131 (36), 102 (12), 77 (7). 1H NMR ($CDCl_3$): 2.15 (3H, *d*, J_{H-F} = 1.86 Hz, CH_3), 4.27 (1H, *dd*, *J* = 2.47 and −14.7 Hz, H_{A-3}), 4.36 (1H, *d*, *J* = −14.7 Hz, H_{B-3}), 4.64 (2H, *d*, J_{H-F} = 47.7 Hz, CH_2F), 7.24–7.72 (*m*, 4H, ArH).

Crystal data

$C_{11}H_{11}FN_2S$
M_r = 222.28
Mo $K\alpha$ radiation
λ = 0.71073 Å
Monoclinic
$P2_1/m$
a = 8.127 (1) Å
b = 6.985 (1) Å
c = 9.306 (2) Å
β = 97.20 (1)°
V = 524.1 (2) Å^3
Z = 2
D_x = 1.408 Mg m^{-3}
D_m not measured
Cell parameters from 32 reflections
θ = 7.5–17°
μ = 0.289 mm^{-1}
T = 293 (2) K
Prismatic
0.40 × 0.30 × 0.20 mm
Colourless

Data collection

Siemens *R3m/V* diffractometer
$2\theta-\omega$ scans
Absorption correction: semi-empirical, ψ scan (Kopfmann & Huber, 1968)
T_{min} = 0.747, T_{max} = 0.784
1795 measured reflections
1304 independent reflections
1117 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.0119
θ_{max} = 27.5°
$h = -11 \rightarrow 11$
$k = -1 \rightarrow 10$
$l = -1 \rightarrow 13$
3 standard reflections monitored every 197 reflections
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0321
$wR(F^2)$ = 0.0894
S = 1.090
1117 reflections
120 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.0430P)^2 + 0.1460P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.208 e Å^{-3}
$\Delta\rho_{min}$ = −0.246 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.042 (7)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S	−0.05274 (7)	1/4	0.84810 (6)	0.0546 (2)
C1	0.1577 (2)	1/4	0.7927 (2)	0.0361 (4)
N2	0.1238 (2)	1/4	0.6343 (2)	0.0336 (4)
C8	−0.0351 (2)	1/4	0.5679 (2)	0.0337 (4)
C9	−0.1648 (2)	1/4	0.6675 (2)	0.0394 (4)
C2	0.2258 (2)	1/4	0.5255 (2)	0.0335 (4)
C7	0.1147 (2)	1/4	0.3964 (2)	0.0337 (4)
N1	−0.0491 (2)	1/4	0.4268 (2)	0.0379 (4)
C3	0.3963 (2)	1/4	0.5258 (2)	0.0443 (5)
C4	0.4547 (3)	1/4	0.3926 (2)	0.0488 (5)
C5	0.3464 (3)	1/4	0.2634 (2)	0.0460 (5)
C6	0.1768 (3)	1/4	0.2631 (2)	0.0412 (5)
C10	0.2462 (2)	0.0690 (3)	0.8492 (2)	0.0501 (4)
F†	0.4085 (4)	0.0785 (6)	0.8421 (4)	0.0788 (10)

† Site occupancy = 0.50.

Table 2. *Selected geometric parameters (Å, °)*

S—C9	1.808 (2)	C2—C3	1.385 (3)
S—C1	1.847 (2)	C2—C7	1.410 (2)
C1—N2	1.465 (2)	C7—N1	1.395 (2)
C1—C10^i	1.516 (2)	C7—C6	1.397 (3)
C1—C10	1.516 (2)	C3—C4	1.382 (3)
N2—C8	1.360 (2)	C4—C5	1.399 (3)

N2—C2	1.387 (2)	C5—C6	1.378 (3)
C8—N1	1.304 (2)	C10—F	1.331 (4)
C8—C9	1.488 (3)		
C9—S—C1	96.69 (9)	C3—C2—C7	122.4 (2)
N2—C1—C10	111.71 (10)	N2—C2—C7	104.2 (2)
N2—C1—S	102.52 (12)	N1—C7—C6	129.8 (2)
C10—C1—S	108.60 (10)	N1—C7—C2	110.7 (2)
C8—N2—C2	106.76 (14)	C6—C7—C2	119.5 (2)
C8—N2—C1	120.38 (15)	C8—N1—C7	103.82 (15)
C2—N2—C1	132.87 (15)	C4—C3—C2	117.0 (2)
N1—C8—N2	114.6 (2)	C3—C4—C5	121.4 (2)
N1—C8—C9	130.4 (2)	C6—C5—C4	121.6 (2)
N2—C8—C9	115.0 (2)	C5—C6—C7	118.1 (2)
C8—C9—S	105.40 (13)	F—C10—C1	111.8 (2)
C3—C2—N2	133.5 (2)		

Symmetry code: (i) $x, \frac{1}{2}-y, z$.

The structure was solved by direct methods and refined using full-matrix least-squares techniques with all non-H atoms anisotropic. The H atoms were located from difference maps and refined isotropically. The C—H bonds range from 1.05 (4) to 0.94 (2) Å, while U_{eq} ranges from 2 (1) to 5.9 (5) Å^2. The space-group determination was a little difficult as there was a choice between $P2_1$ or $P2_1/m$ and neither the systematic absences nor statistical calculations based on the absolute value of E^2-1 could determine which was correct. The best results were obtained in the centrosymmetric space group with the F atom and H10*C* occupancy factors set to 0.5. This is because the central part of the molecule lies on a symmetry mirror plane and the —CH_2F and the —CH_3 groups are positioned symmetrically on either side of the molecule, thus generating the crystallographic disorder.

All calculations were performed on a MicroVAX 3400 and on a DEC-alpha 3000/400.

Data collection: *P3/V Software* (Siemens, 1989). Cell refinement: *P3/V Software*. Data reduction: *SHELXTL-Plus* (Sheldrick, 1990). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus*. Software used to prepare material for publication: *PARST*95 (Nardelli, 1995) and *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1235). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1-[3,5-Bis(trifluoromethyl)phenyl]-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole

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Abstract

The crystal structure of the title compound, $C_{17}H_{10}F_6N_2S$, has been determined. The thiazole ring fused with the benzimidazole system is in an envelope conformation, while the two trifluoromethyl groups at positions 3 and 5 of the phenyl substituent are dynamically disordered because of their rotation along the Csp^3—Csp^2 bond.

Comment

In the course of our studies on new anti-HIV agents, we reported the synthesis and anti-HIV activity of a series of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles, a new class of non-nucleoside HIV-1 reverse transcriptase