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4-(Benzo[*b*]thiophen-3-yl)-1-methylpiperidine-4-carbonitrile

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Key indicators

Single-crystal X-ray study
T = 90 K
Mean σ(C–C) = 0.004 Å
R factor = 0.044
wR factor = 0.098
Data-to-parameter ratio = 13.7

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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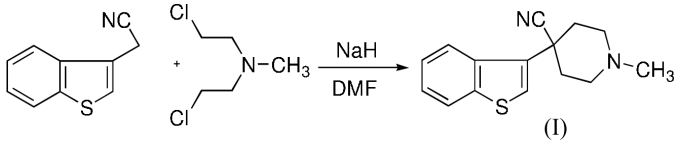
Crystals of the title compound, $C_{15}H_{16}N_2S$, were obtained from the reaction of benzo[*b*]thiophene-3-acetonitrile with mechlorethamine and subsequent crystallization of the product from hexane..

Comment

The piperidine nucleus is present in a wide range of biologically active compounds. For example, the binding properties of 4-diphenylacetoxy-*N*-methylpiperidine methiodide (4-DAMP) and its analogs have been evaluated at muscarinic receptors in human neuroblastoma NB-OK1 cells (M1 receptor subtype), rat heart (M2 subtype), rat pancreas (M3 subtype) and the putative M4 receptor subtype in striatum (Waelbroeck *et al.*, 1992). NMDA receptor antagonist properties of piperidine-2-carboxylic acid derivatives have also been reported (El Hadri *et al.*, 1995). The title compound, (I), is a synthetic precursor of a drug candidate that has been designed as a conformationally restrained benzo[*b*]thiophene-3-ethylamine analog with potential activity as an NMDA receptor antagonist at the polyamine binding site. Compound (I) was prepared by the reaction of benzo[*b*]thiophene-3-acetonitrile with mechlorethamine in the presence of sodium hydride and dimethylformamide (DMF). The structure of the product was initially identified by NMR spectroscopy. To obtain more detailed structural information on the conformation of the molecule in the solid state, the X-ray structure determination of (I) has been carried out and the results are presented here.



(I)

A view of (I) is shown in Fig. 1 and selected geometric parameters are presented in Table 1. The piperidine ring adopts a chair conformation, with the nitrile group at C9 in the axial position, whereas the bulky benzo[*b*]thiophene moiety is located in the equatorial position. Within the piperidine ring system, there are no significant deviations in the tetrahedral bond angles. However, there are deviations in the bond angles within the five-membered ring of the benzo[*b*]thiophene moiety, due to the presence of the S atom. Fig. 2 shows the crystal packing of (I), viewed along the *c* axis.

Experimental

To a suspension of sodium hydride (1.2 g) in DMF (12 ml) at 273 K under a nitrogen atmosphere was added dropwise a solution of benzo[*b*]thiophene-3-acetonitrile (1.386 g, 8 mmol) in DMF (12 ml), while maintaining the temperature at 273 K. After complete addition, the mixture was stirred for 30 min at 273 K. A solution of

mechlorethamine hydrochloride (1.348 g, 7 mmol) in DMF (12 ml) was added dropwise, under nitrogen at 273 K, to the above mixture. The resulting mixture was then stirred at room temperature for 30 min, heated to 353–358 K for 3 h, cooled to room temperature, diluted with ice-cold water, saturated with sodium chloride and extracted with ether (3 × 40 ml). The ether extract was washed with water, extracted with 6 *N* hydrochloric acid (3 × 10 ml) and neutralized with Na_2CO_3. The resultant oil was extracted with ether (3 × 25 ml), dried over anhydrous Na_2SO_4, filtered and evaporated to afford a pale-yellow oil, which immediately solidified to give (I). The crude solid was crystallized from hexane to afford colorless needles, which were suitable for X-ray analysis. ^{1}H NMR ($CDCl_3$): δ 2.17–2.27 (*td*, 2H), 2.41 (*s*, 3H), 2.43–2.5 (*dq*, 2H), 2.54–2.63 (*td*, 2H), 2.97–3.01 (*dd*, 2H), 7.37 (*s*, 1H), 7.38–7.47 (*m*, 2H), 7.87–7.90 (*dd*, 1H), 8.14–8.17 (*dd*, 1H). ^{13}C NMR ($CDCl_3$): δ 35.3, 38.4, 46.4, 52.5, 121.2, 122.8, 123.0, 123.5, 124.5, 124.8, 134.1, 136.0, 141.3.

Crystal data

$C_{15}H_{16}N_2S$
M_r = 256.36
Orthorhombic, $Pca2_1$
a = 18.1809 (4) Å
b = 10.6493 (3) Å
c = 6.8470 (8) Å
V = 1325.67 (16) Å^3
Z = 4
D_x = 1.284 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2635 reflections
θ = 1.0–25.4°
μ = 0.23 mm^{-1}
T = 90.0 (2) K
Rod, colorless
0.25 × 0.10 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
ω scans at fixed χ = 55°
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.945, T_{max} = 0.983
4182 measured reflections
2251 independent reflections
1762 reflections with $I > 2\sigma(I)$
R_{int} = 0.045
θ_{max} = 25.0°
$h = -21 \rightarrow 21$
$k = -12 \rightarrow 12$
$l = -7 \rightarrow 8$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.098
S = 1.05
2251 reflections
164 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Absolute structure: Flack (1983), 976 Friedel pairs
Flack parameter = 0.02 (10)

Table 1
Selected geometric parameters (Å, °).

S1—C2	1.722 (3)	C9—C10	1.542 (4)
S1—C3	1.733 (3)	C10—C11	1.517 (4)
C1—C2	1.347 (4)	C11—N12	1.466 (4)
C1—C9	1.522 (4)	N12—C15	1.455 (4)
C9—C16	1.491 (4)	C16—N16	1.145 (3)
C2—S1—C3	91.07 (14)	C16—C9—C1	109.1 (2)
C2—C1—C8	111.3 (3)	C10—C9—C14	108.3 (2)
C2—C1—C9	123.9 (3)	C15—N12—C13	110.7 (2)
C8—C1—C9	124.8 (3)	C13—N12—C11	109.5 (2)
C1—C2—S1	114.4 (2)	N16—C16—C9	179.1 (3)
C8—C1—C2—S1	0.5 (3)	C9—C1—C2—S1	−178.8 (2)

All H atoms were placed in calculated positions, with C—$H_{methylene}$ = 0.99 Å, C—H_{methyl} = 0.98 Å and C—H = 0.95 Å for all others. H atoms were included in the refinement in the riding-model approximation, with $U_{iso} = 1.2U_{eq}$(C) [$1.5U_{eq}$(C) for methyl].

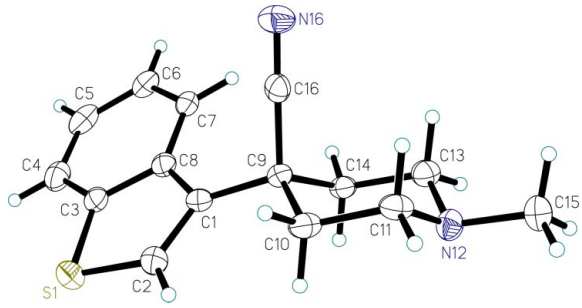


Figure 1
A view of the asymmetric unit of (I), with displacement ellipsoids drawn at the 50% probability level.

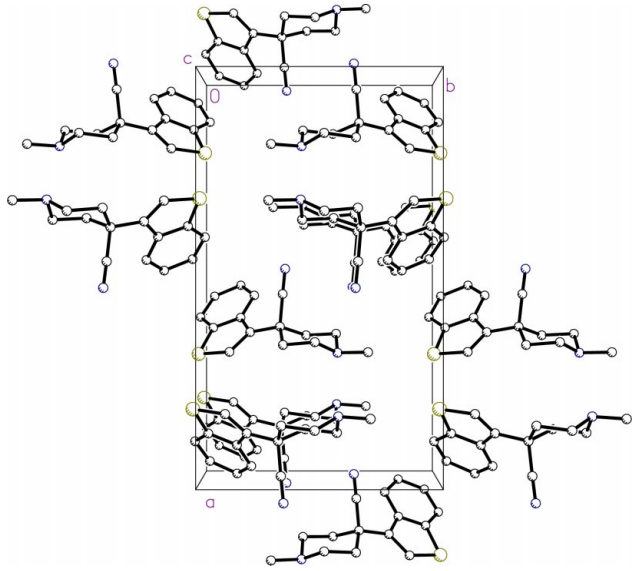


Figure 2
The crystal packing of (I), viewed along the *c* axis. H atoms have been omitted for clarity.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL*97 and local procedures.

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