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(*S*)-2-(Methoxydiphenylmethyl)-1-(thiophen-3-ylmethyl)pyrrolidine

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.006 Å
Disorder in main residue
R factor = 0.044
wR factor = 0.121
Data-to-parameter ratio = 9.0

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

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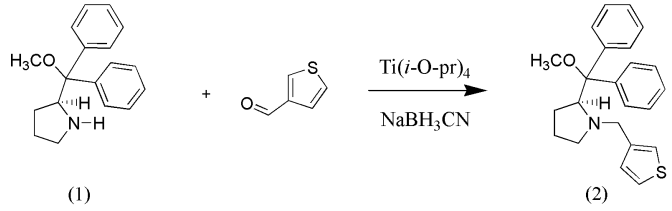
The crystal and molecular structure of the title compound, $C_{23}H_{25}NOS$, has been determined by means of X-ray diffraction. This compound is readily lithiated with *n*-butyllithium at the 2-position of the thiophene ring to give a chiral lithiothiophene that can be used as a chiral template for enantioselective conjugate addition of an alkyl group to an enone.

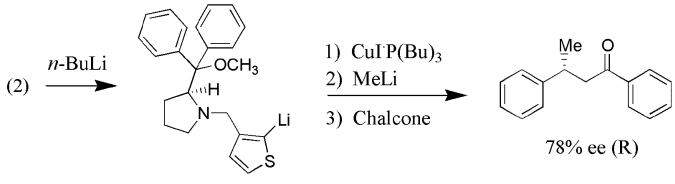
Comment

The title compound, (2), was prepared by the reductive amination (Mattson *et al.*, 1990) of 3-thiophene carboxaldehyde (Huckabee & Stuk, 2001) and the chiral secondary amine, (1), which was prepared from (*S*)-proline following the procedure of Enders *et al.* (1988). The crystals were prepared by cooling an ethanol solution of the compound.



(1) (2)

Compound (2) is readily lithiated at the 2-position of the thiophene ring with *n*-butyllithium to give a chiral lithiophene that is analogous to Nilsson's classic thienyl ligand for enantioselective reaction of an organocuprate with enones (Lindstedt & Nilsson, 1986). The regioselective lithiation by *n*-butyllithium is directed to the 2-position by both the sulfur and the chelating chiral arm. This can be used as a chiral template for enantioselective conjugate addition of an alkyl group to an enone as shown below.



Compound (2) was characterized by standard spectroscopic and physical techniques including NMR, mass spectra, optical rotation and melting point. We were surprised by what appeared to be an anomalous signal in the ^{1}H NMR. There was a multiplet with an integral corresponding to one H atom at 0.3 p.p.m., a region normally reserved for cyclopropyl H atoms. A COSY revealed that the unusual H atom was at the

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4-position of the pyrrolidine ring and *cis* to the ether substituent. Empirical chemical shift calculations for this H atom predict that the resonance should be 1.6 p.p.m. We suspected that the anomalous shift must be due to the ring current from one of the phenyl groups, where that pyrrolidine H atom is placed in the shielding region of the aromatic ring. The crystal structure determination verified the placement of the pyrrolidine H atom (H8*a*) over the phenyl ring. This H atom was measured to be 2.70 Å from the plane of the phenyl ring and 2.82 Å from the center of the ring.

Experimental

Crystal data

$C_{23}H_{25}NOS$
M_r = 363.5
Orthorhombic, $P2_12_12_1$
a = 7.473 (1) Å
b = 8.082 (1) Å
c = 32.600 (5) Å
V = 1968.9 (5) Å^3
Z = 4
D_x = 1.226 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 13.5–21.4°
μ = 1.53 mm^{-1}
T = 298 (2) K
Truncated octahedron, colorless
0.24 × 0.18 × 0.16 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: none
2178 measured reflections
2178 independent reflections
1321 reflections with $I > 2\sigma(I)$
θ_{max} = 69.8°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 39$
3 standard reflections
every 70 reflections
frequency: 56 min
intensity decay: 10%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.121
S = 1.01
2178 reflections
243 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0562P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

The assignment of the *S* absolute configuration was based on our knowledge of the absolute configuration of the starting material, (*S*)-proline, plus the fact that the synthesis reactions were such as to leave this configuration unchanged. The intensity decay of 10% in the standard reflections was both uniform and linear for all three standards. A linear correction to all of the intensities was made based on the linear correction for the decay in the standard reflections. Initial refinement led to difference map peaks and displacement ellipsoids suggestive of a disorder involving the thiophene ring. A disorder model was employed involving rotation of the thiophene ring by 180° about the C1—C2 bond. Final refinement gave occupancy factors of 0.880 (5) for the major component and 0.120 (5) for the minor component. The H atoms were constrained using a riding model. Aromatic C—H distances were fixed at 0.93 Å, the methine C—H length at 0.98 Å, methylene C—H lengths at 0.97 Å, and methyl C—H lengths at 0.96 Å. For the methyl group, an idealized tetrahedral geometry was used, and the torsion angle about the bond to the methyl group was refined. H-atom U_{iso} values were were set at 1.2 times the U_{eq} values of the parent atom, except for the methyl H atoms, for which the factor was 1.5.

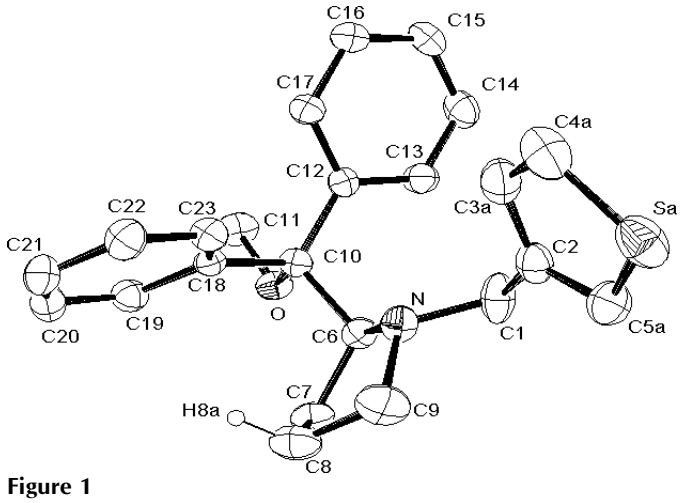

Figure 1
A view of the title compound showing 30% probability displacement ellipsoids. The minor disorder component of the thiophene ring has been omitted for clarity, as have all H atoms except for H8*a*.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

The title compound was synthesized and the crystals prepared by Jason Human and Dr Craig Ogle of the Chemistry Department at The University of North Carolina at Charlotte. We thank the Research Corporation for partial support of this work. This work was also supported, in part, by funds provided by The University of North Carolina at Charlotte.

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