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Methyl 6-bromo-2,3-dihydro-2-methylimidazo[2,1-*b*]oxazole-5-carboxylate

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.005 Å
R factor = 0.040
wR factor = 0.107
Data-to-parameter ratio = 15.4

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

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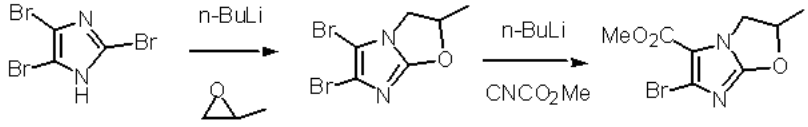
The title novel oxazole derivative, $C_8H_9N_2O_3Br$, is formed by displacement of one of the Br atoms in 5,6-dibromo-2,3-dihydro-2-methylimidazo[2,1-*b*]oxazole using metalation followed by reaction with methylcyanoformate. The cyclic moiety in the molecule is slightly bent from a planar configuration. The shortened distance between the Br atom and oxygen of the carbonyl group of a neighboring molecule is the only significant intermolecular interaction.

Comment

Imidazolones are subunits of a number of natural products including kealiiquinone (Kawasaki *et al.*, 1995), nikkomycin Z (König *et al.*, 1980) and the pyoverdins (Jego *et al.*, 1992). Synthetic imidazolones are also subunits in angiotensin receptor antagonists (Le Bourdonnec *et al.*., 2000), anorectic agents (Poindexter *et al.*, 1999), protein kinase C inhibitors (Karabelas *et al.*, 1999), anticancer agents (Moon *et al.*, 1999) and antimicrobial agents (Solankee *et al.*, 2000). As part of our synthetic approach to kealiiquinone, we needed to generate the anion of an imidazole that could be converted into an imidazolone at a later stage in the synthesis.



(1) (2)

Unfortunately, addition of alkoxides to 2,4,5-tribromoimidazole failed to provide the 2-alkoxy compound. Since intramolecular reactions often occur when intermolecular ones fail, we decided to protect the nitrogen and displace the bromine at C-2 in one step. When 2,4,5-tribromoimidazole was deprotonated with *n*-butyllithium and treated with propylene oxide in THF at 195 K, followed by warming to room temperature, the bicyclic imidazole (1) was generated in 69% yield. A literature search indicated that bromo-methylimidazo[2,1-*b*]oxazoles have not previously been reported. Metalation followed by quenching with methylchloroformate gave the crystalline ester (2). The X-ray structure analysis proves the regiochemistry of the metalation/acylation.

According to the X-ray structure determination of (2) (Fig. 1), atoms C1/C2/C3/C6/N1/N2 are coplanar (r.m.s.d. 0.0076 Å), with atoms O1 and C5 displaced to the same side of this plane [0.088 (5) and 0.196 (7) Å, respectively]. This conformation is very close to the only example of this moiety found in the Cambridge Structural Database (Allen, 2002), for 2,3-dihydro-5-nitroimidazo[2,1-*b*]oxazole (Brown *et al.*, 1979).

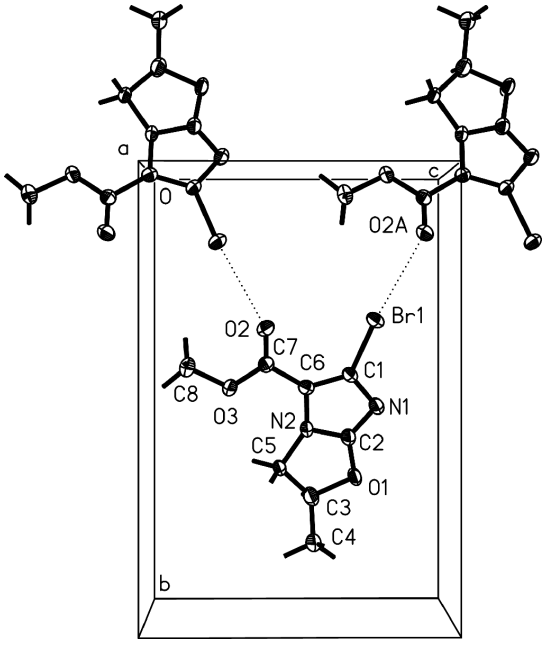


Figure 1
A perspective view of ribbon motif of (2) with the atomic numbering scheme for the basic molecule. Displacement ellipsoids are drawn at the 50% probability level. The intermolecular interactions Br1$\cdots$O2($x, \frac{1}{2}-y, \frac{1}{2}+z$) are shown as dashed lines.

The dihedral angle between the above-mentioned plane and O2—C7—O3—C8 (r.m.s. deviation = 0.0018 Å) is 7.5 (2)°. The C4 displacement ellipsoid is significantly elongated; this may be an indication of the preferred direction of thermal motion of the terminal Me group.

The packing consists of infinite zigzag ribbons along the *c* axis, linked by an intermolecular Br1$\cdots$O2($x, \frac{1}{2}-y, \frac{1}{2}+z$) interaction with a distance of 3.009 (3) Å, which is significantly shorter than the sum of the van der Waals radii, 3.37 Å (Bondi, 1964).

The X-ray structure analysis of (2) proves the regiochemistry of the metalation/acylation. The detailed structure of (2) will guide our efforts to extend the scope of this useful reaction.

Experimental

Preparation of 5,6-dibromo-2,3-dihydro-2-methylimidazo[2,1-*b*]oxazole, (1): to a solution of 2,4,5-tribromoimidazole (10 g, 32.78 mmol) in dry THF (50 ml), *n*-BuLi (1 equivalent) was added dropwise at 195 K. After 0.75 h propylene oxide (10 equivalent) was added to the reaction and stirring was continued during warming from 195 K to room temperature over 48 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 100 ml), dried, and the organic phase was concentrated *in vacuo* to furnish a crude red oil which was purified by SGC (silica gel flash chromatography) using 1:1 hexane–ethyl acetate. The yield of product was 69% (6.4 g). Compound (1): mp 333–335 K; IR (neat): 2984, 1566, 1490, 1188 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 (3 H, *d, J* = 6.1 Hz), 3.68 (1 H, *dd, J* = 9.3, 7.7 Hz), 4.20 (1 H, *dd, J* = 9.4, 7.9 Hz), 5.30–5.41 (1 H, *m*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.1, 50.3, 83.3, 92.6, 114.1, 157.2; HRMS: *m*/*z* found 281.8830, $C_6H_6Br_2N_2O$ requires 281.8826.

Preparation of (2): to a solution of (1) (1 equivalent) in dry THF, *n*-BuLi (1 equivalent in hexanes) was added dropwise at 195 K. After 0.75 h, methylcyanoformate in THF solution was added at 195 K. The reaction was quenched with saturated NH_4Cl solution after 1 h and extracted with ethyl acetate. After removal of the solvent, the crude residue was purified by SGC using hexanes–ethyl acetate to provide (2) in 92% yield. Compound (2): m.p. 450–452 K; IR (neat): 2960, 1710, 1556, 1524, 1223, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63 (3 H, *d, J* = 6.4 Hz), 3.85 (3 H, *s*), 3.91–3.95 (1 H, *m*), 4.45–4.51 (1 H, *m*), 5.37–5.48 (1 H, *m*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 51.8, 52.1, 84.6, 115.2, 123.7, 159.3, 159.4; HRMS: *m*/*z* found 259.9799, $C_8H_9BrN_2O_3$ requires 259.9796.

Crystal data

$C_8H_9BrN_2O_3$	Mo $K\alpha$ radiation
M_r = 261.08	λ = 0.71073 Å
Monoclinic, $P2_1/c$	Cell parameters from 684 reflections
a = 7.1338 (13) Å	θ = 2.6–28.1°
b = 13.981 (3) Å	μ = 4.34 mm^{-1}
c = 9.4670 (15) Å	T = 173 (2) K
β = 90.614 (5)°	Plate, colorless
V = 944.1 (3) Å^3	0.24 × 0.22 × 0.09 mm
Z = 4	
D_x = 1.837 Mg m^{-3}	

Data collection

Bruker SMART1000 CCD diffractometer	1958 independent reflections
φ scans	1701 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)	R_{int} = 0.039
T_{min} = 0.402, T_{max} = 0.676	θ_{max} = 28.2°
3396 measured reflections	$h = -5 \rightarrow 9$
	$k = -18 \rightarrow 10$
	$l = -11 \rightarrow 5$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0495P)^2 + 1.5689P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.040	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.107	$\Delta\rho_{max}$ = 1.10 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.64 e Å^{-3}
1958 reflections	
127 parameters	
H-atom parameters constrained	

All H atoms were positioned geometrically and refined as riding atoms, with isotropic displacement parameters set at $1.2U_{eq}$ or $1.5U_{eq}$ of the parent atoms. The distances to H atoms are in the range 0.98–0.99 Å. The highest peak is located 0.96 Å from the Br atom

Data collection: *SMART* (Bruker, 2001); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2002); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

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