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Ethyl 5-(5-oxo-2,3-dihydro-5*H*-oxazolo[2,3-*a*]-isoindol-9b-ylmethyl)-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)isoxazole-3-carboxylate: the product of a novel synthetic method

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Key indicators

Single-crystal X-ray study
T = 85 K
Mean σ(C–C) = 0.002 Å
R factor = 0.048
wR factor = 0.117
Data-to-parameter ratio = 17.1

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

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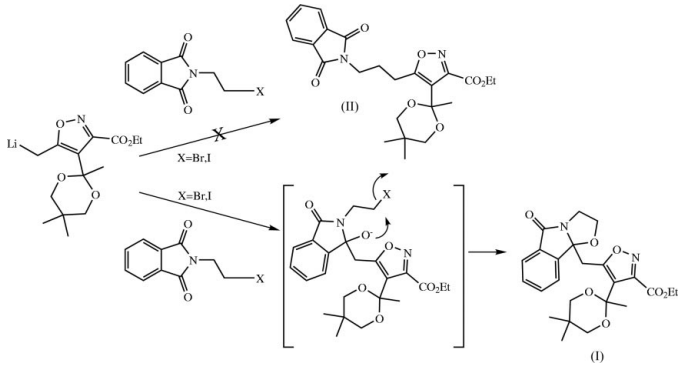
The title compound, $C_{24}H_{28}N_2O_7$, is the product of a novel synthetic procedure in which a highly functionalized heterocycle is formed. The crystal packing involves dimers, utilizing non-classical weak C—H···O interactions (*ca* 3.36–3.46 Å) and an antiparallel π–π interaction between two of the pseudo-aromatic isoxazole moieties. These dimers are associated into a three-dimensional network *via* further non-classical hydrogen bonding.

Comment

As part of our continuing research into isoxazoles (*e.g.* Burkhart *et al.*, 2004; Nelson *et al.*, 2003), the title compound, (I), has been prepared and its structure determined.



The molecule (Fig. 1) forms a weakly associated dimer *via* non-classical hydrogen bonds between C14 and O3^{i} (see Table 1). The dimers are arranged with the isoxazole rings parallel to the (010) plane. These rings are, however, antiparallel to each other. This orientation results in π–π interactions between the weakly aromatic isoxazole rings with a centroid–centroid distance of 3.677 Å (see Fig. 2). This is similar to other isoxazole systems that also have π–π interactions (*e.g.* Shen *et al.*, 2004). These dimers are linked by further weak hydrogen bonding (C12···O6^{ii}, see Table 1) into a complex three-dimensional network (Fig. 3).

Nucleophilic reactions with haloalkylphthalimides are, in principle, complicated by the competing electrophilic centers, namely the carbon bearing the halogen, and the imide carbonyl moieties. Our research indicates that for this particular nucleophile, and when *X* = Br or I, reaction occurs exclusively at the carbonyl carbon (as determined by ^{1}H NMR of the crude reaction mixture), and is followed by displacement of the halide by the resultant oxide. This is shown in the scheme. To the best of our knowledge, this reactivity profile (selectivity for carbonyl attack even when *X* = I) has never

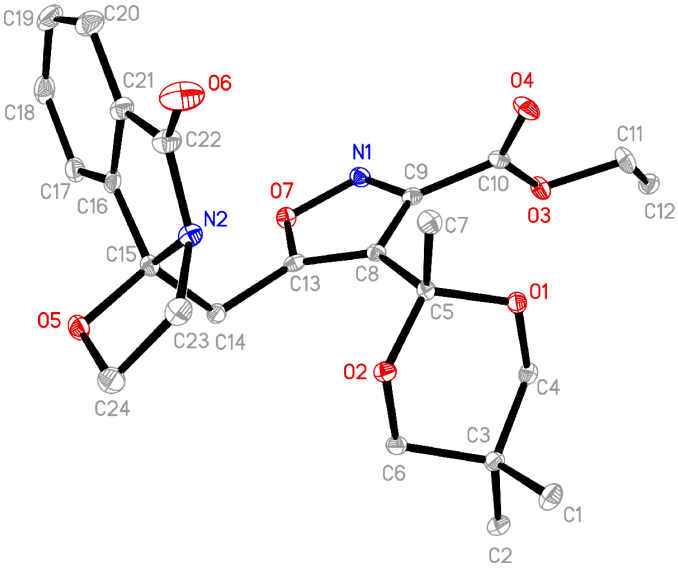


Figure 1
The molecular structure of (I), showing 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

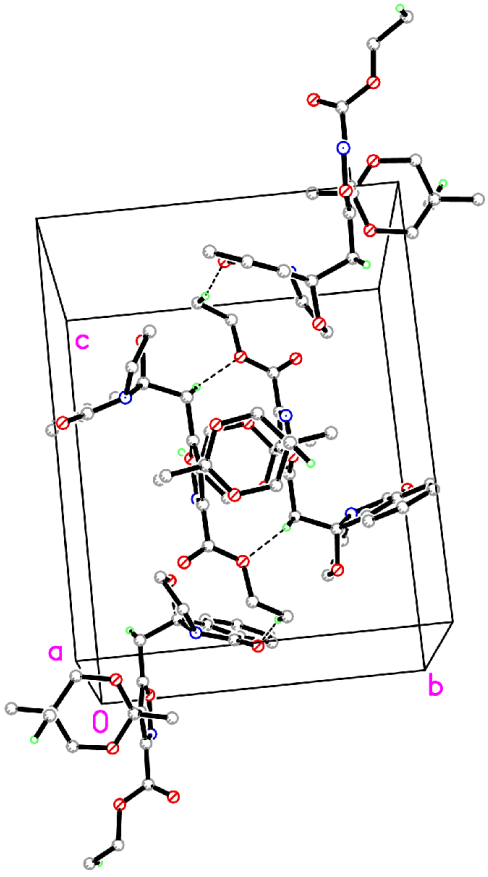


Figure 2
Packing diagram of (I), showing the antiparallel arrangement of the isoxazole dimers. Only H atoms involved in hydrogen bonding (dashed lines) are shown.

been observed previously. It may be possible to effect the alternative route by modifying the reaction conditions, though no such precedent has been found in the literature.

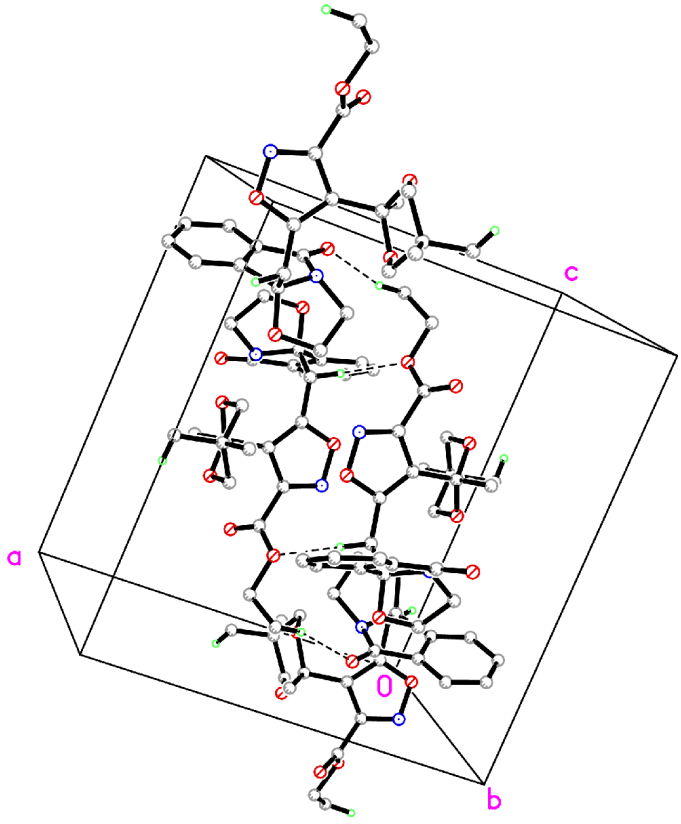


Figure 3
Alternate view of the hydrogen-bonded dimers, also showing the extended three-dimensional hydrogen bonding (dashed lines). Only H atoms involved in hydrogen bonding are shown.

Experimental

n-BuLi in hexanes (1.94 mmol, 2.05 *M*, 0.95 ml) was added to a solution of diisopropylamine (1.94 mmol, 0.27 ml) in tetrahydrofuran (THF) under argon at 273 K. The solution was stirred for 20 min, cooled to 195 K and then transferred *via* a cannula into a solution of ethyl 5-methyl-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)isoxazole-3-carboxylate (Zhou & Natale, 1998) (1.76 mmol, 500 mg) in THF (40 ml) under argon that was already cooled to 195 K. The mixture was stirred for 15 min. A separate flask was charged with the electrophile [2-(2-iodoethyl)-1*H*-isoindole-1,3(2*H*)-dione, 2.11 mmol, 636 mg] and THF (10 ml), then cooled to 195 K. The electrophile solution was then added dropwise *via* a cannula, at a rate such that the reaction temperature did not rise above 200 K. The reaction was stirred for 2 h, then allowed to slowly come to room temperature. Saturated NH_4Cl(aq) (30 ml) was added and the solution was concentrated under reduced pressure. The residue was extracted with EtOAc (2 × 50 ml). The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (3:1 hexane–ethyl acetate), and recrystallized from hexanes to afford the desired product as colorless prisms in 70% yield (m.p. 434–435 K) ^{1}H NMR: *d* 0.66 (*s*, 3H), 1.20 (*s*, 3H), 1.38 (*t*, 3H, *J* = 7.1 Hz), 1.67 (*s*, 3H), 3.30 (*m*, 5H), 3.55 (*d*, 1H, *J* = 14.6 Hz), 3.73 (*d*, 1H, *J* = 14.6 Hz), 3.99 (*m*, 1H), 4.17 (*m*, 2H), 4.39 (*q*, 2H, *J* = 7.1 Hz), 7.62 (*m*, 3H), 7.77 (*d*, 1H, *J* = 7.5 Hz). ^{13}C NMR: *d* 14.8, 22.7, 23.3, 30.5, 30.6, 34.2, 43.9, 63.4, 70.7, 72.6, 72.7, 97.1, 99.8,

117.6, 123.8, 125.3, 131.5, 134.4, 146.7, 157.3, 162.3, 165.7, 174.3. MS (FAB) *m*/*z*: 457 (*M* + 1), 371, 174.

Crystal data

$C_{24}H_{28}N_2O_7$	D_x = 1.352 Mg m^{-3}
M_r = 456.48	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 5056 reflections
a = 13.302 (3) Å	θ = 2.2–27.6°
b = 11.707 (2) Å	μ = 0.10 mm^{-1}
c = 14.412 (3) Å	T = 85 (2) K
β = 91.76 (3)°	Prism, colorless
V = 2243.3 (8) Å^3	0.24 × 0.14 × 0.13 mm
Z = 4	

Data collection

Bruker–Siemens SMART APEX diffractometer	5153 independent reflections
ω scans	3773 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)	R_{int} = 0.045
T_{min} = 0.976, T_{max} = 0.987	θ_{max} = 27.6°
17 860 measured reflections	$h = -16 \rightarrow 17$
	$k = -15 \rightarrow 15$
	$l = -12 \rightarrow 18$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0555P)^2 + 0.2378P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.048	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.117	$\Delta\rho_{max}$ = 0.38 e Å^{-3}
S = 1.03	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
5153 reflections	
302 parameters	
H-atom parameters constrained	

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C14—H14B···O3^{i}	0.99	2.52	3.466 (2)	159
C12—H12C···O6^{ii}	0.98	2.40	3.357 (2)	164

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

All H atoms were positioned geometrically (C—H = 0.95–0.99 Å) and refined using a riding model, with U_{iso} constrained to be 1.2U_{eq} of the carrier atom.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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