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Reactive intermediates in peptide synthesis: the *N*-oxysuccinimido ester of N^{α}-*para*-toluenesulfonyl-α-amino-isobutyric acid

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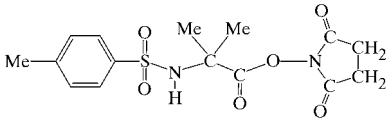
The preparation, characterization, and molecular and crystal structures of succinimido 2-(tosylamino)isobutyrate, $C_{15}H_{18}N_2O_6S$, are described. The succinimido ring is nearly orthogonal to the ester group.

Comment

X-ray diffraction has been shown to be an excellent technique for contributing to our understanding of α-amino acid chemistry (Toniolo & Benedetti, 1991). However, reactive intermediates in peptide synthesis are commonly characterized by low melting points and poor crystallinities. Using an appropriate combination of a high molecular weight aromatic N^{α}-protecting group [*e.g.* the *para*-toluenesulfonyl (Tos) group] and a conformationally restricted α-amino acid (*e.g.* a $C^{\alpha,\alpha}$-disubstituted glycine, such as Aib, α-aminoisobutyric acid), known to exhibit a higher tendency to crystallize than protein residues, this drawback may be easily overcome.



(I)

We describe here the synthesis, characterization, and results of a crystallographic analysis of Tos–Aib–OSu (OSu is oxysuccinimide), or succinimido 2-(tosylamino)isobutyrate, (I). Among the variety of N^{α}-protected α-amino acid hydroxylamine derivatives reported in the literature, one of the most popular methods for activation of the COOH function in peptide synthesis, namely the formation of *N*-oxysuccinimido esters (Anderson *et al.*, 1964), has been extensively exploited because: (i) the water-soluble by-product *N*-hydroxysuccinimide can be easily removed by extraction, and (ii) it allows amide bond formation with no racemization (epimerization), even if a peptide segment is activated (Benoiton *et al.*, 1995). The only X-ray diffraction structure published for an *N*-oxysuccinimido ester of an amino acid or peptide is Boc–L-Val–OSu (Boc is *tert*-butyloxycarbonyl) (Sukumar *et al.*, 1993).

In Tos–Aib–OSu (Fig. 1), the C11═O3 bond length (Table 1) is close to that typical of carboxylic esters (Allen *et al.*, 1987). Atoms C8, C11, O3 and O4 of the ester group are coplanar within 0.030 (2) Å, while atom N2 is displaced from the ester plane by 0.189 (2) Å.

The pentaatomic succinimido ring is slightly puckered towards the $^4T_3$ (twist) disposition, as indicated by the values of the puckering parameters (relative to the N2—C12—C13—C14—C15 atom sequence) of q_2 = 0.095 (2) Å and φ_2 = −94.2 (13)° (Cremer & Pople, 1975). Such a ring conformation is characterized by a local pseudo-twofold axis along N2 and the midpoint of the C13—C14 bond. The characteristic O4—N2 bond is 1.391 (2) Å. The value of the Δ/σ ratio between the two N—Csp^2 bond lengths, 4.01, is just significant. The internal bond angles of the succinimido moiety have values in the range 104.9 (2)–106.2 (1)°, as expected for a pentagonal ring, with the exception of the bond angle at nitrogen (Table 1). The exocyclic bond angles involving the two carbonyl O atoms are remarkably expanded, and lie in the range 124.1 (2)–130.8 (2)°, and the C11—O4—N2 bond angle is wide (Table 1). The dihedral angle between the average –C(O)O– ester and succinimido planes is nearly orthogonal, 105.2 (1)°, presumably to reduce potential lone-pair repulsion between O3 and the carbonyl O5 and O6 atoms. The O3···O5 and O3···O6 distances are 3.255 (3) and 3.834 (3) Å, respectively. A similar succinimido geometry has been reported for Boc–L-Val–OSu (Sukumar *et al.*, 1993).

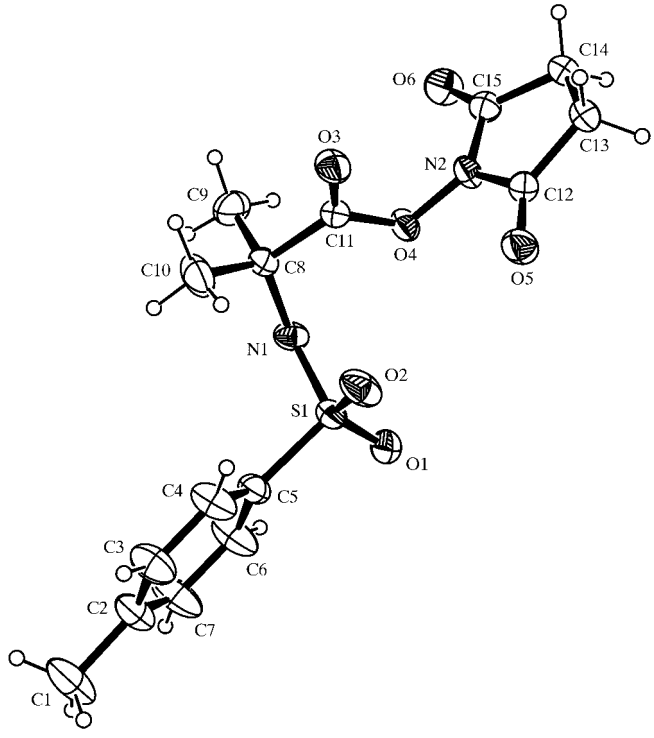


Figure 1
A view of the title molecule with the atom-numbering scheme. Displacement ellipsoids are shown at the 30% probability level and H atoms are represented by spheres of arbitrary radii.

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The S1—N1—C8—C11 and N1—C8—C11—O4 amino acid backbone torsion angles are 65.5 (2) and 33.2 (2)°, respectively. These values confirm the propensity of Aib for the helical region of the conformational map (Karle & Balaram, 1990; Toniolo & Benedetti, 1991). The conformationally sensitive Aib τ (N1—C8—C11) bond angle (Paterson *et al.*, 1981) is close to the regular tetrahedral value (Table 1). The C5—S1—N1—C8 torsion angle is close to 90°, its value being 97.64 (18)°. Significantly short intramolecular distances between non-bonded atoms are O2···C11 of 2.938 (3) Å and O2···O4 of 3.140 (3) Å. The S1 atom is 2.746 (2) Å from C8, 3.291 (4) Å from C10 and 3.325 (2) Å from C11. The dihedral angle between the planes of the Tos aromatic ring and the ester –C(O)O– group is 149.1 (1)°, while that involving the Tos aromatic ring and the succinimido moiety is 128.4 (1)°.

In the crystal, the molecules form dimers stabilized by double intermolecular hydrogen bonds between (sulfonamido) N1—H1 groups and (succinimido) O6═C15 groups of symmetry-related molecules. The N1···O6^{i} distance and N1—H···O6^{i} angle [symmetry code: (i) $1-x, 1-y, 2-z$; Table 2] are within accepted ranges (Görbitz, 1989).

Experimental

For the synthesis of Tos–Aib–OSu, Tos–Aib–OH (Leplawy *et al.*, 1960) (386 mg, 1.5 mmol) and *N*-ethyl-*N*′-[(3-dimethylamino)-propyl]carbodiimide hydrochloride (288 mg, 1.5 mmol) were dissolved at 273 K in acetonitrile (5 ml) in the presence of *N*-hydroxysuccinimide (173 mg, 1.5 mmol) and *N*-methylmorpholine (0.165 ml, 1.5 mmol). The reaction mixture was stirred for 1 h at 273 K and for a further 3 h at room temperature. The solvent was evaporated and the residue was taken up in ethyl acetate and washed successively with 0.5 *M* citric acid, water, 5% $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The title compound was obtained in 73% yield from ethyl acetate–petroleum ether (1:3) as a colourless solid with a melting point of 448–449 K. TLC: R_F ($CHCl_3$/ethanol, 9:1) = 0.85; IR (KBr): 3309, 1811, 1778, 1731 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83–7.26 (4H, 4 × aromatic CH), 5.27 (1H, Aib NH), 2.84 (4H, 2 × OSu CH_2), 2.42 (3H, Tos CH_3), 1.64 (6H, 2 × Aib CH_3). Single crystals were obtained from ethyl acetate/petroleum ether by vapour diffusion.

Crystal data

$C_{15}H_{18}N_2O_6S$
M_r = 354.37
Triclinic, $P\overline{1}$
a = 9.094 (2) Å
b = 12.575 (2) Å
c = 8.3520 (10) Å
α = 93.03 (3)°
β = 115.84 (3)°
γ = 93.97 (3)°
V = 853.9 (3) Å^3
Z = 2
D_x = 1.378 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 48 reflections
θ = 7–12°
μ = 0.22 mm^{-1}
T = 293 (2) K
Prism, colourless
0.40 × 0.40 × 0.40 mm

Data collection

Philips PW1100 diffractometer
θ–2θ scans
4129 measured reflections
4111 independent reflections
2635 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 28.0°
$h = -12 \rightarrow 10$
$k = -16 \rightarrow 16$
$l = 0 \rightarrow 11$
3 standard reflections
every 50 reflections
intensity decay: none

Table 1
Selected geometric parameters (Å, °).

S1—N1	1.617 (2)	O6—C15	1.208 (3)
O3—C11	1.180 (2)	N1—C8	1.464 (3)
O4—N2	1.391 (2)	N2—C15	1.380 (3)
O4—C11	1.398 (2)	N2—C12	1.397 (3)
O5—C12	1.194 (2)	C8—C11	1.536 (3)
N2—O4—C11	112.2 (2)	O5—C12—N2	124.3 (2)
C15—N2—C12	116.4 (2)	O5—C12—C13	130.8 (2)
N1—C8—C11	111.4 (2)	N2—C12—C13	104.9 (2)
O3—C11—O4	122.5 (2)	O6—C15—N2	124.1 (2)
O3—C11—C8	126.4 (2)	O6—C15—C14	130.0 (2)
O4—C11—C8	110.8 (2)	N2—C15—C14	105.9 (2)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O6^{i}	0.86	2.15	2.964 (2)	159

Symmetry code: (i) $1-x, 1-y, 2-z$.

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.142
S = 1.03
4111 reflections
217 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0774P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.47 e Å^{-3}

All H atoms were placed at idealized positions and refined as riding (N—H = 0.86 Å and C—H = 0.93–0.97 Å).

Data collection, cell refinement and data reduction: *FEBO* (Belletti, 1993); structure solution: *SHELXS*97 (Sheldrick, 1997); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *PARST*96 (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1559). Services for accessing these data are described at the back of the journal.

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