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1,3-Thiazolidine derivatives from regioselective [2+3]-cycloadditions of azomethine ylides with thioketones

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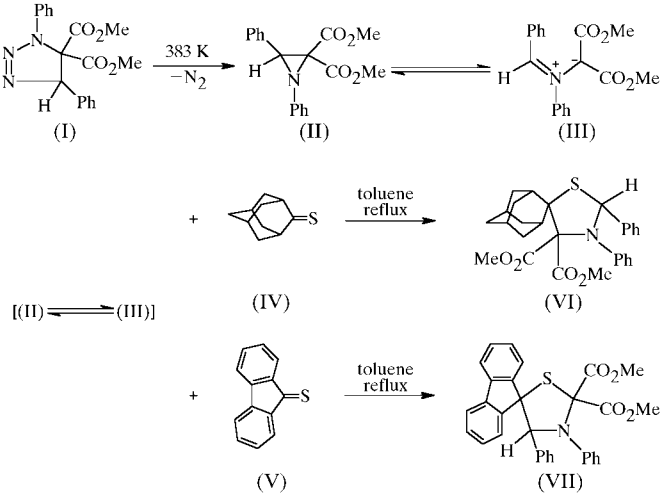
The title compounds, namely dimethyl (2*RS*)-2,3-diphenyl-1,3-thiazolidine-5-spiro-2′-adamantane-4,4-dicarboxylate methanol solvate, $C_{28}H_{31}NO_4S\cdot0.275CH_4O$, and dimethyl (4*RS*)-3,4-diphenyl-1,3-thiazolidine-5-spiro-9′-(9′*H*-fluorene)-2,2-dicarboxylate, $C_{31}H_{25}NO_4S$, were obtained from dipolar [2+3]-cycloadditions of an azomethine ylide with adamantanethione and thiofluorenone, respectively. The structures show that the choice of thioketone affects the regioselectivity of the cycloaddition. The asymmetric unit of the former structure contains two molecules of the thiazolidine derivative plus a site for a partial occupancy (55%) methanol molecule. O—H···O and C—H···O interactions link two of each of these entities into closed centrosymmetric hexamers. The five-membered ring in each structure has an envelope conformation.

Comment

1,3-Thiazolidines may be used in the synthesis of pharmaceuticals such as immunomodulating drugs or antibiotics (Hwu *et al.*, 1999; Pellegrini *et al.*, 1999). Thioketones are recognized as 'superdipolarophilic' compounds and combine smoothly with 1,3-dipoles to yield sulfur-containing five-membered heterocycles (Huisgen *et al.*, 1995). However, only a few papers have dealt with the reactions of azomethine ylides with thioketones. Heating 1,2,3-triazoline, (I), with adamantane-2-thione, (IV), or 9*H*-fluorene-9-thione, (V), in boiling toluene, resulted in the formation of 1,3-thiazolidines (VI) or (VII), respectively (Mlostoń & Skrzypek, 1990) (see *Scheme*). The molecular formulae of $C_{28}H_{31}NO_4S$ for (VI) and $C_{31}H_{25}NO_4S$ for (VII) were established from elemental analyses and mass spectra. Desulfurization of (VII) with Raney nickel resulted unexpectedly in ring contraction and the formation of the corresponding azetidine derivative (Mlostoń *et al.*, 2000, 2002). On the other hand, the same procedure with (VI) led to recovery of the starting material, which suggested that the formation of (VI) and (VII) had occurred with different regioselectivity. X-ray crystallographic analyses of (VI) and (VII) were undertaken to elucidate their structures and thereby determine the influence of the location of the ester groups on the course of the subsequent desulfurization reaction. The two structures (Figs. 1 and 2) confirm that the regioselectivity of the addition step leading to the formation of the heterocyclic ring from thioketones and azomethine ylide (III) is dependent on the type of thioketone used (see *Scheme*).



The asymmetric unit of compound (VI) contains two independent molecules of the thiazolidine derivative plus a site for a methanol molecule which is approximately 55% occupied. Although the unit cell is metrically very close to orthorhombic, tests with *PLATON* (Spek, 2003) indicated the absence of any additional crystallographic symmetry. The two symmetry-independent thiazolidine molecules have the same

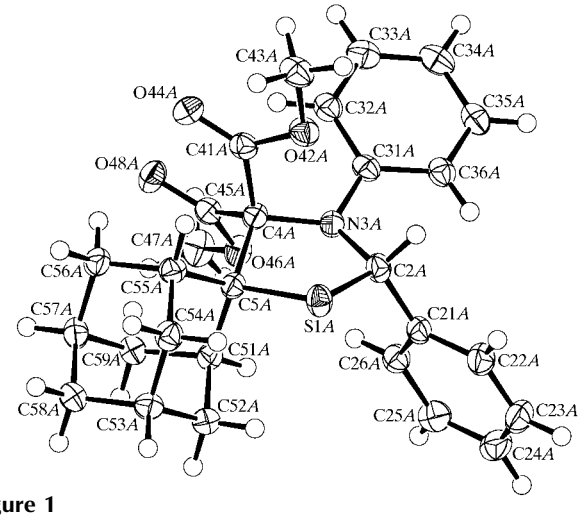


Figure 1
View of one of the two symmetry-independent 1,3-thiazolidine molecules of (VI), showing the atom-labelling scheme, with displacement ellipsoids at the 50% probability level. H atoms are represented by circles of arbitrary radii.

† Deceased.

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configuration and almost identical conformations. The weighted r.m.s. fit (Mackay, 1984) of the atoms from the two molecules is 0.18 Å and the two molecules are related by a rotation of approximately 175°. Compound (VII) crystallizes with just one independent molecule in the asymmetric unit. The bond lengths and angles in the two structures are generally in good agreement with expected values (Allen *et al.*, 1987), although in (VI), the C4*A*—C5*A* and C4*B*—C5*B* bonds are quite long, at about 1.61 Å, and the S—C bond lengths are asymmetric (Table 1). As a consequence of the long C—C bonds, the C2*A*—N3*A*—C4*A* and C2*B*—N3*B*—C4*B* bond angles are larger than the corresponding angles in compound (VII), where the C4—C5 bond is not unduly long and the S—C bonds are more symmetrical (Table 3). Elongation of C—C bonds in the range 1.56–1.61 Å has been observed frequently in spirocyclic thiazolidine, thiazole, oxathiolane and dithiolane ring systems (Linden *et al.*, 1998). Steric crowding is probably responsible for the observed geometry of the thiazolidine ring in compound (VI). There are several very short intramolecular contacts between the H atoms of the adamantanyl group and the ester C and O atoms, as well as with the thiazolidine S atom. The shortest contacts of this type are 2.29 and 2.31 Å for H591···C45*A* and H593···C45*B*, respectively, which are approximately 0.6 Å shorter than the sum of the van der Waals radii of these atoms, and three other H···C or H···S contacts in each of the independent molecules are between 0.37–0.51 Å shorter than the sum of the van der Waals radii. The steric constraints introduced by the adamantanyl group also severely restrict the orientations that can be adopted by the ester substituents, which results in additional short intramolecular contacts, namely O44*A*···O48*A* [2.7221 (16) Å], O44*B*···O48*B* [2.7415 (18) Å], O42*A*···N3*A* [2.6230 (17) Å], O46*A*···N3*A* [2.6094 (16) Å], O42*B*···N3*B* [2.6001 (18) Å] and O46*B*···N3*B* [2.5896 (16) Å]. By contrast, the less bulky planar fluorenyl substituent in compound (VII) is not involved in any unduly short intramolecular contacts and the bond lengths and angles within the thiazolidine ring are consequently less distorted than in compound (VI).

The 1,3-thiazolidine rings of both compounds have envelope conformations. For compound (VI), the puckering parameters (Cremer & Pople, 1975) are q_2 = 0.3953 (14) and 0.4549 (14) Å, and φ_2 = 146.7 (2) and 150.87 (19)° for the rings defined by the atom sequences S1*A*—C2*A*—N3*A*—C4*A*—C5*A* and S1*B*—C2*B*—N3*B*—C4*B*—C5*B*, respectively, and the envelope flaps are formed by the spiro-C atoms C5*A* and C5*B*, respectively. For compound (VII), the puckering parameters are q_2 = 0.4592 (9) Å and φ_2 = 110.25 (10)° for the atom sequence S1—C2—N3—C4—C5, with atom C4 forming the envelope flap.

The phenyl substituents at atoms C2*A* and C2*B* of compound (VI) occupy pseudo-axial positions, while those at atoms N3*A* and N3*B*, as well as all the phenyl substituents in compound (VII), occupy pseudo-equatorial positions. In compound (VII), the planes of both phenyl substituents lie almost perpendicular to the mean plane of the 1,3-thiazolidine ring, with interplanar angles of 61.06 (4) and 65.14 (3)° for the phenyl substituents at N3 and C4, respectively. The planes of the phenyl substituents at atoms C2*A* and C2*B* of compound (VI) are aligned similarly, with the corresponding interplanar angles being 75.39 (5) and 72.04 (5)°, respectively. In contrast, the planes of the phenyl substituents at atoms N3*A* and N3*B* of compound (VI) lie almost parallel to the planes of the respective 1,3-thiazolidine rings, with interplanar angles of 21.30 (8) and 21.67 (8)°.

The fluorene substituent in compound (VII) is almost planar, although slight envelope puckering of the central five-membered ring pushes the spiro-C5 atom out of the plane and gives the entire fluorene moiety a flat-dish shape. Excluding atom C5, the r.m.s. deviation of atoms C51 to C62 from their

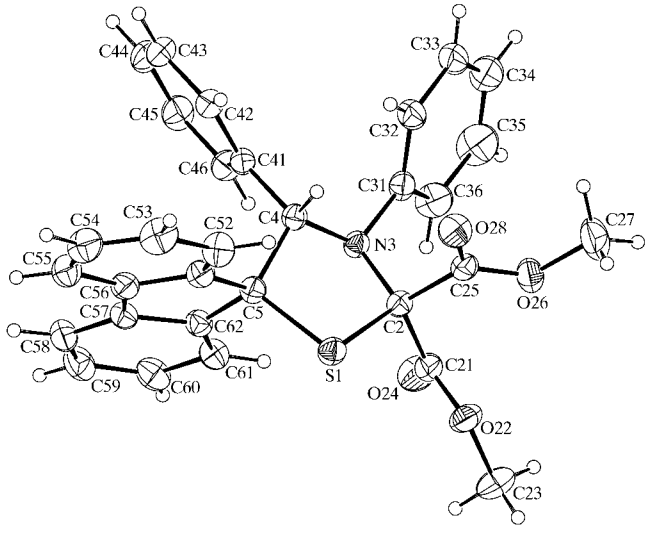

Figure 2
View of the molecule of (VII), showing the atom-labelling scheme, with displacement ellipsoids at the 30% probability level. H atoms are represented by circles of arbitrary radii.

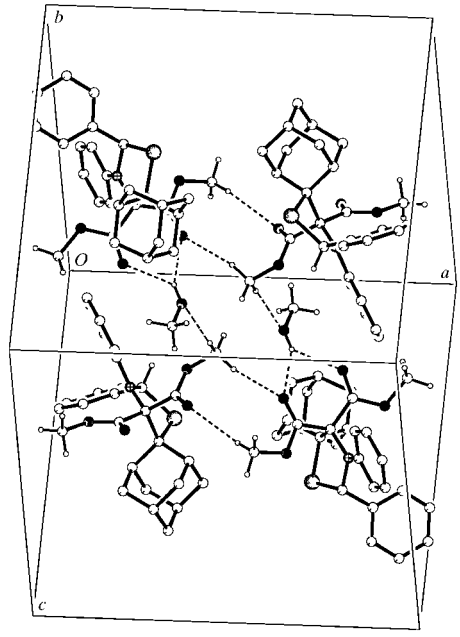

Figure 3
View of the hexamer formed by the intermolecular O—H···O and C—H···O interactions (dashed lines) in the structure of (VI). All H atoms, apart from those of the methyl and hydroxy groups, have been omitted for clarity.

mean plane is 0.040 Å, with a maximum deviation of 0.0638 (9) Å for atom C51. Atom C5 lies 0.1896 (11) Å from this plane. The flatness of the dish is shown by the angle of intersection between the two phenyl rings of the fluorene moiety, which is 4.50 (7)°.

In compound (VI), the hydroxy group of the methanol molecule forms bifurcated intermolecular hydrogen bonds with both of the ester carbonyl O atoms of a neighbouring thiazolidine molecule, although one interaction is significantly weaker then the other (Table 2). These interactions form a six-membered loop with a graph-set motif of $R_1^2(6)$ (Bernstein *et al.*, 1995). Two intermolecular C—H···O interactions link the independent thiazolidine molecules to each other and a third interaction links one of these molecules to a neighbouring methanol molecule. The combination of O—H···O and C—H···O interactions links two of each of the independent thiazolidine molecules and two methanol molecules into a closed centrosymmetric hexameric unit (Fig. 3). Compound (VII) does not display any significant intermolecular C—H···O interactions.

Table 1
Selected geometric parameters (Å, °) for (VI).

S1*A*—C2*A*	1.8144 (16)	S1*B*—C2*B*	1.8087 (16)
S1*A*—C5*A*	1.8413 (16)	S1*B*—C5*B*	1.8400 (16)
C2*A*—N3*A*	1.464 (2)	C2*B*—N3*B*	1.463 (2)
N3*A*—C4*A*	1.4612 (19)	N3*B*—C4*B*	1.4619 (19)
C4*A*—C5*A*	1.609 (2)	C4*B*—C5*B*	1.613 (2)
C2*A*—S1*A*—C5*A*	95.23 (7)	C2*B*—S1*B*—C5*B*	94.02 (7)
N3*A*—C2*A*—S1*A*	106.17 (10)	N3*B*—C2*B*—S1*B*	105.93 (10)
C4*A*—N3*A*—C2*A*	116.81 (12)	C4*B*—N3*B*—C2*B*	116.51 (12)
N3*A*—C4*A*—C5*A*	108.06 (12)	N3*B*—C4*B*—C5*B*	107.02 (12)
C4*A*—C5*A*—S1*A*	100.87 (10)	C4*B*—C5*B*—S1*B*	99.93 (10)
S1*A*—C2*A*—C21*A*—C26*A*	100.57 (16)	S1*B*—C2*B*—C21*B*—C26*B*	109.83 (15)
C2*A*—N3*A*—C31*A*—C36*A*	23.5 (2)	C2*B*—N3*B*—C31*B*—C36*B*	21.7 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O61—H61···O44*A*	0.85 (4)	2.03 (4)	2.788 (3)	148 (4)
O61—H61···O48*A*	0.85 (4)	2.43 (4)	3.099 (3)	136 (4)
C43*A*—H433···O44*B*	0.98	2.54	3.375 (2)	144
C43*B*—H436···O44*A*	0.98	2.49	3.439 (2)	162
C43*B*—H434···O61^{i}	0.98	2.33	3.215 (3)	151

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

Experimental

Compounds (VI) and (VII) were obtained by the dipolar [2+3]-cycloaddition of the azomethine ylide (III), generated *in situ* by the thermal ring opening of dimethyl 1,3-diphenylaziridine-2,2-dicarboxylate, (II), with adamantanethione, (IV), and thiofluorenone, (V), respectively (Mlostoń & Skrzypek, 1990; Mlostoń *et al.*, 2002). Suitable crystals were obtained by slow evaporation of methanol solutions of the compounds at room temperature; m.p. = 423 and 476 K for (VI) and (VII), respectively.

Compound (VI)

Crystal data

$C_{28}H_{31}NO_4S\cdot0.275CH_4O$
M_r = 486.43
Monoclinic, $P2_1/n$
a = 15.6658 (2) Å
b = 18.1538 (3) Å
c = 17.2513 (3) Å
β = 90.2397 (6)°
V = 4906.12 (13) Å^3
Z = 8
D_x = 1.317 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 11 543 reflections
θ = 2.0–27.5°
μ = 0.17 mm^{-1}
T = 160 (1) K
Prism, colourless
0.35 × 0.18 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
76 328 measured reflections
11 220 independent reflections
7745 reflections with $I > 2\sigma(I)$
R_{int} = 0.071
θ_{max} = 27.5°
$h = 0 \rightarrow 20$
$k = 0 \rightarrow 23$
$l = -22 \rightarrow 22$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.110
S = 1.02
11217 reflections
641 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0462P)^2 + 0.6825P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0024 (3)

Compound (VII)

Crystal data

$C_{31}H_{25}NO_4S$
M_r = 507.58
Triclinic, $P\overline{1}$
a = 9.817 (1) Å
b = 11.233 (2) Å
c = 12.459 (2) Å
α = 102.53 (1)°
β = 97.91 (1)°
γ = 98.52 (1)°
V = 1305.7 (4) Å^3
Z = 2
D_x = 1.291 Mg m^{-3}
D_m = 1.249 Mg m^{-3}
D_m measured by flotation in KBr and KI
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 20.0–21.3°
μ = 0.16 mm^{-1}
T = 293 (2) K
Prism, colourless
0.8 × 0.7 × 0.5 mm

Data collection

Rigaku AFC-5*S* diffractometer
ω scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
T_{min} = 0.897, T_{max} = 0.937
18 942 measured reflections
9471 independent reflections
6330 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 32.6°
$h = -14 \rightarrow 14$
$k = -17 \rightarrow 17$
$l = -18 \rightarrow 18$
3 standard reflections
every 150 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.121
S = 1.06
9471 reflections
337 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0687P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.045 (3)

Table 3
Selected geometric parameters (Å, °) for (VII).

S1—C2	1.8338 (10)	N3—C4	1.4722 (11)
S1—C5	1.8232 (9)	C4—C5	1.5540 (13)
C2—N3	1.4734 (11)		
C5—S1—C2	93.89 (4)	N3—C4—C5	105.01 (7)
N3—C2—S1	106.14 (6)	C4—C5—S1	102.24 (6)
C4—N3—C2	109.65 (7)		
C2—N3—C31—C36	81.56 (12)	C5—C4—C41—C46	−85.97 (11)

The asymmetric unit of (VI) contains two molecules of the adamantanyl derivative plus one site for a methanol molecule which is partially occupied. A common site-occupation factor for the atoms of the methanol molecule initially refined to a value close to 0.55. In the final refinement, this site-occupation factor was held fixed at 0.55. The position of the hydroxy H atom of the methanol molecule in (VI) was located in a difference Fourier map and its position was refined freely along with an isotropic displacement parameter. In both structures, the methyl H atoms were constrained to an ideal geometry [C—H = 0.98 Å for (VI) and 0.96 Å for (VII)], with U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about the parent C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H distances in the range 0.93–1.00 Å and U_{iso}(H) = 1.2U_{eq}(C). Three low-angle reflections were omitted from the final cycles of refinement of (VI) because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop.

For compound (VI), data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). For compound (VII), data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1989); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1989); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). For both compounds, program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL*97 and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1163). Services for accessing these data are described at the back of the journal.

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