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Ethyl 2-({6-amino-2-(benzylsulfanyl)-5-[2-(ethoxycarbonyl)prop-2-enyl]pyrimidin-4-yloxy}methyl)acrylate

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.002 Å
Disorder in main residue
R factor = 0.040
wR factor = 0.091
Data-to-parameter ratio = 14.7

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

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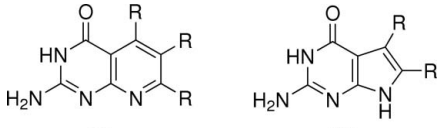
A new synthesis of carbon–carbon bonds at the 5-position of 2-thiosubstituted pyrimidines *via* the Claisen rearrangement is reported. A direct route towards the synthesis of carbon bonds at the 5-position of 2-thiobenzyl pyrimidines when reacted with ethyl 2-(bromomethyl)acrylate at 328 K delivered the unexpected title compound, $C_{23}H_{27}N_3O_5S$. Structural elucidation showed this compound to have undergone *O*-allylation followed by *ortho*-Claisen rearrangement and subsequent secondary *O*-allylation with excess ethyl 2-(bromomethyl)acrylate. Disorder about the centre of symmetry allows it to exist as two conformers with different orientations of the phenyl group.

Comment

In order to extend and illustrate our endeavours to develop further the C-5 carbon–carbon bond formation of 2-thiosubstituted pyrimidines (Huggan *et al.*, 2005; La Rosa *et al.*, 2002) we sought to utilize the Claisen rearrangement (Claisen & Tietze, 1925) within the context of designing routes towards the synthesis of pyrido[2,3-*d*]-pyrimidines, (I), and pyrrolo[2,3-*d*]-pyrimidines, (II), as potential inhibitors of enzymes in the folic acid biosynthesis pathway. When an N atom is present at the 2-position, the formation of C—C bonds at the 5-position is relatively straightforward. However, our solid phase route (Gibson *et al.*, 2003) utilizes an S atom at the 2-position and previous attempts at C—C bond formation in solution phase with sulfur at the 2-position have proved unsuccessful.

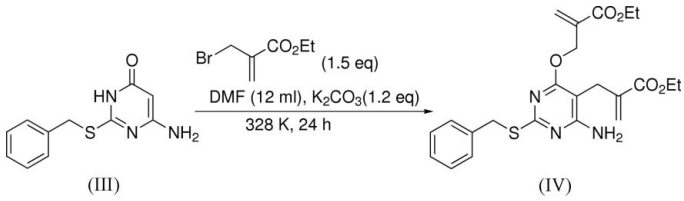


(I) (II)

where R = aryl, allyl or H

Structurally related folic acid antagonists (Taylor *et al.*, 1983) have been shown to possess a range of biological properties, such as antitumour (Grivsky *et al.*, 1980), antibacterial (Matsumoto & Minami, 1975) and antifungal (Heckler *et al.*, 1991) activity, and hence their efficient synthesis, along with the synthesis of other novel compounds, would be advantageous. The commercially available 6-amino-2-mercaptopyrimidin-4(3*H*)-one was reacted with benzyl mercaptan to yield 6-amino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone, (III) (90%). Compound (III) was then reacted with ethyl 2-(bromomethyl)acrylate to give products, from which

the title compound, (IV), was surprisingly isolated and identified.



The molecular structure of (IV) is shown in Fig. 1, and selected bond distances and angles are given in Table 1. As can be seen in Fig. 1, structural elucidation showed this compound to have been formed through *O*-allylation followed by *ortho*-Claisen rearrangement and subsequent secondary *O*-allylation with excess ethyl 2-(bromomethyl)acrylate.

Disorder about a centre of symmetry allows (IV) to exist as two conformers with different orientations of the phenyl group. An alternative solution in the non-centrosymmetric space group *P*1 was rejected as the disorder was still present. The two vinyl groups adopt different geometries. The torsion angles C13—C12—C14—O4 and C7—C6—C8—O2 [−13.1 (2) and 176.8 (2)°, respectively] indicate the *syn* and *anti* relationship of the vinyl and ketone groups and, whilst the presence of O1 allows the C7-centred group to bo coplanar with the heterocyclic ring, the absence of an equivalent atom forces the C13-centred substituent out of this plane. A search of the Cambridge Structural Database (Version 5 with updates to October 2005; Allen, 2002) found 140 similar non-cyclic vinyl fragments and indicated that the geometric parameters of (IV) (Table 1) are all within normal ranges. A similar search showed that the geometry of the hetrocyclic fragment is also in agreement with the known literature.

In the crystal structure of (IV) both the amine H atoms form hydrogen bonds with atoms O4 and N2 of symmetry-related molecules acting as acceptors (Table 2). This results in the formation of hydrogen-bonded chains of molecules.

Experimental

Compound (III) (0.69 g, 2.95 mmol) was dissolved in dimethylformamide (12 ml, anhydrous) at room temperature under nitrogen. Ethyl 2-(bromomethyl)acrylate (610 µl, 4.40 mmol, 1.5 equivalents) and K_2CO_3 (0.50 g, 3.62 mmol, 1.2 equivalents) were added and the reaction was stirred in an oil bath at 328 K for 24 h. Once the reaction was complete (by thin-layer chromatography) the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane, extracted with brine, and then collected, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The title compound (IV) was separated by column chromatography using ethyl acetate/hexane (1:1) as eluant, and was isolated as a white solid (0.114 g, 0.25 mmol, 8%). Crystals of (IV) were grown by slow recrystallization from methanol at room temperature (m.p. 383–385 K). IR (KBr): 3407, 3323, 3191, 1707, 1652, 1572, 1555, 1493, 1474, 1444, 1427, 1401, 1376, 1353, 1316, 1280, 1264, 1227, 1158, 1123, 1050, 1027, 855, 776, 708 cm^{-1}; LC–MS: (*M*+1) = 458.3; ^{1}H NMR (DMSO-d_6): δ 7.41–7.39 [2H, *m*, 2 × C(2)H], 7.31–7.19 [3H, *m*, 2 × C(3)H, 1 × C(1)H], 6.19 (2H, *br s*, NH2), 6.19 [1H, *s*, C(18A)H], 5.99 [1H, *s*, C(12B)H], 5.75 [1H, *s*, C(12A)H], 5.14 [1H, *s*, C(18B)H], 4.98 [2H, *s*, C(16)H2], 4.29 [2H, *s*, C(5)H2], 4.20–4.09 [4H, *d* of *q*, 1 × 2H, *q*, C(20)H, 1 × 2H, *q*, C(14)H], 3.33 [2H, *s*, C(10)H2], 1.26–1.15 [6H, *d* of *t*, 1 × 3H, *t*, C(21)H, 1 × 3H, *t*, C(15)H]; ^{13}C NMR (DMSO-d_6): δ 166.39 (C-19), 166.18 (C-13), 165.44 (C-7), 164.75 (C-6), 163.39 (C-9), 138.66 (C-4), 137.02 (C-17), 136.31 (C-11), 128.77 (C-2), 128.28 (C-3), 126.82 (C-1), 126.08 (C-12), 123.07 (C-18), 90.74 (C-8), 63.49 (C-16), 60.49 (C-20), 60.34 (C-14), 33.83 (C-5), 24.39 (C-10), 14.04 (C-15), 13.91 (C-21).

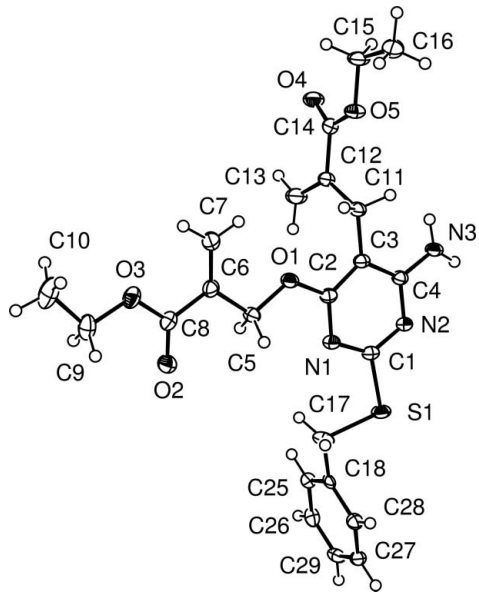


Figure 1
Molecular structure of (IV), with displacement ellipsoids drawn at the 50% probability level. Only one position of the disordered benzyl unit is shown for clarity.

Crystal data

$C_{23}H_{27}N_3O_5S$	Z = 2
M_r = 457.54	D_x = 1.344 Mg m^{-3}
Triclinic, $P\overline{1}$	Mo $K\alpha$ radiation
a = 7.3668 (2) Å	Cell parameters from 5141 reflections
b = 11.5842 (3) Å	θ = 1.0–27.5°
c = 14.5700 (4) Å	μ = 0.18 mm^{-1}
α = 111.692 (2)°	T = 123 (2) K
β = 99.520 (2)°	Prism, colourless
γ = 93.076 (2)°	0.45 × 0.15 × 0.10 mm
V = 1130.44 (5) Å^3	

Data collection

Nonius KappaCCD diffractometer	R_{int} = 0.044
φ and ω scans	θ_{max} = 27.5°
Absorption correction: none	$h = -9 \rightarrow 9$
25883 measured reflections	$k = -15 \rightarrow 13$
5178 independent reflections	$l = -18 \rightarrow 18$
3777 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0315P)^2 + 0.4141P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.040	
$wR(F^2)$ = 0.091	
S = 1.04	$(\Delta/\sigma)_{max}$ = 0.001
5178 reflections	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
353 parameters	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected geometric parameters (Å, °).

O2—C8	1.2094 (18)	C2—C3	1.386 (2)
O4—C14	1.2153 (19)	C3—C4	1.407 (2)
N1—C1	1.3341 (19)	C6—C7	1.313 (2)
N1—C2	1.3424 (18)	C6—C8	1.484 (2)
N2—C1	1.3317 (19)	C12—C13	1.318 (2)
N2—C4	1.3611 (18)	C12—C14	1.496 (2)
N3—C4	1.347 (2)		
C1—N1—C2	113.72 (13)	N1—C2—C3	125.47 (14)
C1—N2—C4	116.39 (13)	C2—C3—C4	114.93 (13)
N2—C1—N1	128.05 (13)	N2—C4—C3	121.35 (14)
C5—O1—C2—N1	−5.5 (2)	C13—C12—C14—O4	−13.1 (2)
C7—C6—C8—O2	176.82 (19)	C1—S1—C17—C18	160.97 (14)
C4—C3—C11—C12	96.68 (18)	C1—S1—C17—C19	−85.22 (17)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H1N···O4^{i}	0.872 (18)	2.133 (19)	2.9832 (18)	164.8 (16)
N3—H2N···N2^{ii}	0.883 (19)	2.20 (2)	3.0868 (19)	176.8 (17)

Symmetry codes: (i) $-x, -y-1, -z$; (ii) $-x, -y, -z$.

After several trial calculations, the disordered CH_2Ph group was modelled over two sites each with occupancy 0.5. The methylene H atoms of this group were found in a difference synthesis and then constrained to ride on the parent C atom. The amine H atoms were refined freely, but all other H atoms were positioned geometrically at distances of 0.95 (CH and vinyl CH_2), 0.98 (CH_3) or 0.99 Å (CH_2) from the parent C atoms; a riding model was used [U_{iso}(H) = $1.5U_{eq}$(C) for CH_3 and U_{iso}(H) = $1.2U_{eq}$(C) for all others] during refinement.

Data collection: *COLLECT* (Hooft, 1998) and *DENZO* (Otwinowski & Minor, 1997); cell refinement: *DENZO*; data reduction: *DENZO*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

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