Acta Crystallographica Section C
**Crystal Structure Communications**
ISSN 0108-2701

# Ethyl 2-{[2-(3-nitrophenyl)-5-phenyl-1*H*-imidazol-4-yl]sulfanyl}acetate: synthesis *via* a microwave-mediated combinatorial chemistry approach

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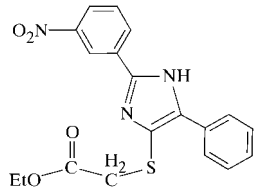
Received 22 November 2001
Accepted 29 November 2001
Online 13 February 2002

The orange title compound, $C_{19}H_{17}N_3O_4S$, can be synthesized either *via* microwave-mediated combinatorial chemistry strategies or conventional synthetic procedures. The phenyl and *meta*-nitrophenyl $C_6$ rings are essentially coplanar with the central imidazolyl ring, with interplanar angles of 0.87 (5) and 0.97 (4)°, respectively, resulting in optimum conjugation ($SCH_2$ moiety included); $\lambda_{max}$ = 281 nm in $CH_3CN$. The principal intermolecular interactions are $N_{imid}—H\cdots O_{nitro}$ and $N_{imid}—H\cdots O{=}C$ [$N\cdots O$ = 3.058 (2) and 3.432 (3) Å, and $N—H\cdots O$ = 128 and 153°, respectively]. The closest $H\cdots S$ distance is an intramolecular $C—H\cdots S$ contact, with $H\cdots S$ = 2.54 Å and $C—H\cdots S$ = 136°.

## Comment

The development of high-throughput biological screening has led to dramatic changes in the drug-discovery process. The generation of large numbers of new drug-like molecules has been achieved in a combinatorial manner rather than in a traditional sequential fashion. The exploitation of microwave irradiation for organic synthesis has gained in popularity, with dramatic reduction in reaction times being reported for a wide range of organic reactions (Caddick, 1995; Strauss & Trainor, 1995; Galema, 1997). Clearly, the ability of microwave technology to synthesize organic compounds rapidly would be of significant benefit for combinatorial library generation, and its potential as a future tool for drug-discovery programs has recently been identified (Larhed & Hallberg, 2001).

Substituted 4(5)-sulfanylimidazoles have been synthesized in a three-component reaction of an aldehyde, alkyl bromide, 2-oxothioacetamide and ammonium acetate. Parallel libraries have been generated using both conventional and new microwave approaches; full synthetic details for compound (I), $C_{19}H_{17}N_3O_4S$, *via* both routes are described in the *Experimental* section. The principal benefit of the microwave-facilitated procedure over the conventional procedure was a reduction in the overall library generation time from 12 h to 16 min. The microwave library generation utilized an array of expandable reaction vessels which can accommodate the increased pressure build-up during the reaction (Coleman *et al.*, 2002).




(I)

The molecular structure of (I) is depicted with the atomic numbering scheme in Fig. 1, with selected geometric dimensions given in Table 1. Bond lengths are in accord with the anticipated values (Orpen *et al.*, 1994). Comparisons with a related monosubstituted 2-imidazol-2-yl derivative (Gallagher *et al.*, 1998) indicate that the imidazolyl bond lengths expand slightly in (I) on extra substitution. A *para*-fluorophenylacetamide analogue has been deposited as a private communication (Gallagher *et al.*, 2001) in the Cambridge Structural Database (CSD; Allen & Kennard, 1993).

In (I), the phenyl and *meta*-nitrophenyl $C_6$ rings are essentially coplanar with the central imidazolyl ring [dihedral angles 0.87 (5) and 0.97 (4)°, respectively], resulting in an optimum conjugation in the system ($SCH_2$ moiety included, Fig. 1); $\lambda_{max}$ = 281 nm in $CH_3CN$ solution. Two principal intermolecular interactions are present in the crystal structure of (I) and both involve the imidazolyl N2—H2 donor as (i) the N2—H2···O21 interaction, which generates a one-dimensional chain along [101], in combination with (ii) the longer N2—H2···O1($1-x$, $-y$, $1-z$) interaction, which further impacts on the overall hydrogen-bonding network by forming $\pi\cdots\pi$ stacked aromatic columns (Table 2).

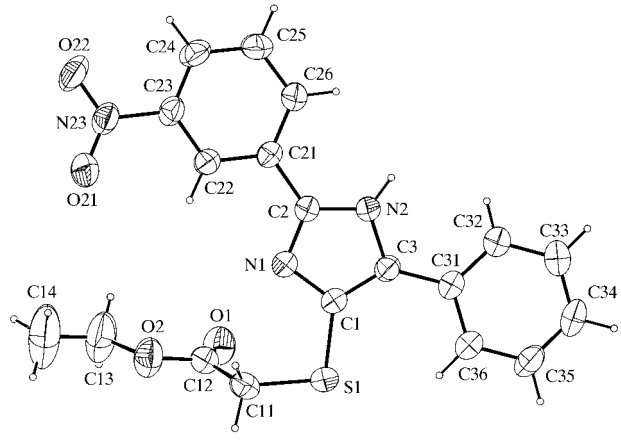



**Figure 1**
A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

 DOI: 10.1107/S0108270101020571  

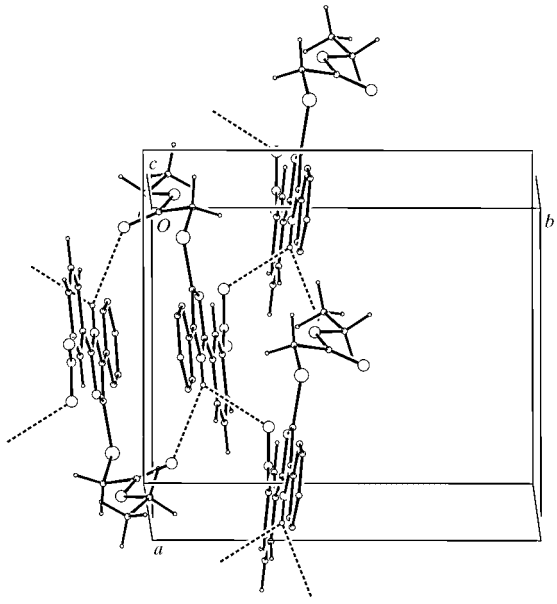



**Figure 2**
A view of the interactions and $\pi\cdots\pi$ stacking in the crystal structure. The terminal phenyl ring H atoms have been removed for clarity.

Thus, the central imidazolyl ring core stacks about inversion centres along the *b* axis, with the centroids [$Cg1\cdots Cg1(1-x, -y, 1-z)$] 3.56 Å apart and with a perpendicular separation of 3.36 Å (Fig. 2). For the three coplanar aromatic rings, the perpendicular stacking distance between planes is between 3.35 and 3.43 Å, with a dihedral angle between the stacked planes of <2°. This is similar in nature to the $\pi\cdots\pi$ stacking in graphite, where the interplanar spacing is 3.35 Å (Wells, 1984).

A search of the CSD using *ConQuest* (Version 1.2, April 2001) for systems containing the 2-(3-nitrophenyl)-1*H*-imidazolyl group reveals eight structures, most of which contain two *para*-methoxyphenyl groups attached at the remaining two imidazolyl C atoms. 4,5-Bis(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-imidazole, (II) (Inouye & Sakaino, 2000; CSD refcode CIZMUT01), is representative. From a series of solvates, different coloured crystals of (II) were obtained and the resulting bathochromic shifts explained by molecular planarity and charge-transfer effects. A related search for the $S-C_3N_2H$ moiety revealed six structures quite different to (I) where the sulfur has been incorporated in a heterocyclic ring or is part of a metal complex; a wider search for 2-thioimidazolyl, $SC_3N_2$, yielded a total of 41 compounds. For comparison with (I), 1-benzyl-5-methoxycarbonylmethylthio-4-nitroimidazole, ($C_{13}H_{13}N_3O_4S$; Saadeh *et al.*, 1995) contains $C_{imid}-S-C_{ester}$ bond lengths of 1.740 and 1.799 Å, a C—S—C angle of 101.14° and a C—S—C—C torsion angle of −72.1°, which are similar to the data for (I) in Table 1. The related S—C—$C_{imid}$ and S—C—$N_{imid}$ angles are 134.8 and 122.0°, respectively.

Previous biological screening of substituted sulfanylimidazoles has shown their potential as acyl–CoA:cholesterol acyltransferase inhibitors, analgesic agents and angiotensin II receptor antagonists (Higley *et al.*, 1994; Sharpe *et al.*, 1985; Deprez *et al.*, 1995).

## Experimental

2-Oxo-2-phenylthioacetamides were prepared according to literature methods (Asinger & Gentz, 1963). The combinatorial library was generated using an Argonaut first mate synthesiser with reaction components aldehyde (0.15 mmol), ammonium acetate (0.15 mmol) and 2-oxo-2-arylthioacetamide (0.15 mmol) loaded into each reaction vessel with 2 ml of $C_2H_5OH$. The library was heated for 12 h, cooled, products precipitated with 1 *M* HCl (5 ml), filtered and dried to give an average library purity and yield of 78 and 63%. An identical library was generated using microwave irradiation to give an average library purity and yield of 76 and 67%.

An alternative but conventional synthesis for {[2-(3-nitrophenyl)-5-phenyl-1*H*-imidazol-4-yl]sulfanyl}acetic acid ethyl ester is as follows: a mixture of 2-oxo-2-phenylthioacetamide (1.04 g, 6.3 mmol), sodium carbonate (0.67 g, 6.3 mmol), ammonium acetate (0.59 g, 6.3 mmol), ethyl bromoacetate (1.05 g, 6.3 mmol) and 3-nitrobenzaldehyde (0.95 g, 6.3 mmol) in ethanol (50 ml) was heated under reflux for 7 h under nitrogen. The reaction mixture was concentrated to half its volume and an orange–yellow solid precipitated. Further purification using dry flash chromatography on silica gel with a gradient of ether–hexane–methanol 2:8:1 to 8:2:1 gave the pure product (1.59 g, 78%; m.p. 462–464 K).

Orange crystals were obtained by slow evaporation of a methanol solution. UV–vis: $\lambda_{max}$ = 281, 315 nm. IR ($\nu_{C=O}$ $cm^{-1}$): 1728 (KBr). $^1$H NMR (300 MHz, $\delta$, $d_6$ DMSO): 1.07 (*t*, 3H), 3.82 (*s*, 2H), 3.95 (*q*, 2H), 7.37 (*m*, 1H), 7.48 (*m*, 2H), 7.80 (*m*, 1H), 7.90 (*m*, 2H), 8.24 (*m*, 1H), 8.47 (*m*, 1H), 8.92 (*m*, 1H). HRMS calculated 383.0940, found 383.0932. Analysis calculated for $C_{19}H_{17}N_3O_4S$: C 59.58, H 4.47, N 10.97, S 8.37%; found: C 59.39, H 4.39, N 10.92, S 8.87%.

*Crystal data*

| | |
|---|---|
| $C_{19}H_{17}N_3O_4S$ | $D_x$ = 1.406 Mg $m^{-3}$ |
| $M_r$ = 383.42 | Mo $K\alpha$ radiation |
| Monoclinic, $P2_1/n$ | Cell parameters from 70 reflections |
| $a$ = 10.5606 (13) Å | $\theta$ = 5.4–15.6° |
| $b$ = 12.1254 (9) Å | $\mu$ = 0.21 $mm^{-1}$ |
| $c$ = 14.8196 (10) Å | $T$ = 292 (1) K |
| $\beta$ = 107.389 (6)° | Block, orange |
| $V$ = 1810.9 (3) Å$^3$ | 0.45 × 0.35 × 0.18 mm |
| $Z$ = 4 | |

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| S1—C1 | 1.759 (2) | N2—C2 | 1.350 (2) |
| S1—C11 | 1.787 (2) | N2—C3 | 1.390 (2) |
| O1—C12 | 1.201 (3) | C1—C3 | 1.376 (3) |
| O2—C12 | 1.326 (3) | C2—C21 | 1.469 (3) |
| O2—C13 | 1.451 (3) | C3—C31 | 1.460 (3) |
| N1—C1 | 1.366 (2) | C11—C12 | 1.503 (3) |
| N1—C2 | 1.324 (2) | C13—C14 | 1.422 (4) |
| | | | |
| C1—S1—C11 | 100.18 (9) | N1—C2—C21 | 123.72 (17) |
| S1—C11—C12 | 115.70 (15) | N2—C2—C21 | 125.01 (17) |
| S1—C1—N1 | 120.12 (14) | C2—N2—C3 | 108.46 (15) |
| S1—C1—C3 | 127.98 (15) | C1—C3—N2 | 103.31 (16) |
| N1—C1—C3 | 111.90 (17) | C1—C3—C31 | 133.95 (18) |
| C1—N1—C2 | 105.05 (16) | N2—C3—C31 | 122.73 (17) |
| N1—C2—N2 | 111.27 (16) | | |
| | | | |
| C1—S1—C11—C12 | 70.19 (18) | N1—C2—C21—C22 | 0.2 (3) |
| S1—C11—C12—O2 | −168.09 (15) | C1—C3—C31—C36 | 0.9 (4) |
| C11—S1—C1—N1 | −6.30 (19) | | |

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N2—H2···O21$^{i}$ | 0.86 | 2.46 | 3.058 (2) | 128 |
| N2—H2···O1$^{ii}$ | 0.86 | 2.64 | 3.432 (3) | 153 |
| C36—H36···S1 | 0.93 | 2.54 | 3.271 (2) | 136 |

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

*Data collection*

Bruker *P*4 diffractometer
$\omega$ scans
4517 measured reflections
3524 independent reflections
2569 reflections with $I > 2\sigma(I)$
$R_{int} = 0.016$
$\theta_{max} = 26.0°$
$h = -1 \rightarrow 13$
$k = -1 \rightarrow 14$
$l = -18 \rightarrow 17$
4 standard reflections
every 296 reflections
intensity variation: 1%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.110$
$S = 1.03$
3524 reflections
245 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0496P)^2 + 0.459P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.21$ e Å$^{-3}$
$\Delta\rho_{min} = -0.18$ e Å$^{-3}$

All H atoms bound to C atoms were treated as riding, with *SHELXL*97 (Sheldrick, 1997) defaults for C—H lengths and with $U_{iso}(H) = 1.5U_{eq}(C)$ for methylene-H atoms and $1.2U_{eq}(C)$ for the remainder. Examination of the structure with *PLATON* (Spek, 1998) showed that there were no solvent-accessible voids in the crystal lattice.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1998); software used to prepare material for publication: *SHELXL*97 and *PREP*8 (Ferguson, 1998).

JFG thanks Dublin City University for the purchase of a *P*4 diffractometer. DFOS thanks Enterprise Ireland for grants in aid of research.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1525). Services for accessing these data are described at the back of the journal.

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