Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Three 4,7-diaryl-2-ethylsulfanyl-pyrazolo[1,5-*a*][1,3,5]triazines

Henry Insuasty,[a] Paola Mier,[a] Gina Suarez,[a] John N. Low,[b] Justo Cobo[c] and Christopher Glidewell[d]*

[a]Departamento de Química, Universidad de Nariño, Cuidad Universitaria Torobajo, AA 1175 Pasto, Colombia, [b]Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen AB24 3UE, Scotland, [c]Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain, and [d]School of Chemistry, University of St Andrews, Fife KY16 9ST, Scotland
Correspondence e-mail: cg@st-andrews.ac.uk

Received 27 November 2007
Accepted 28 November 2007
Online 22 December 2007

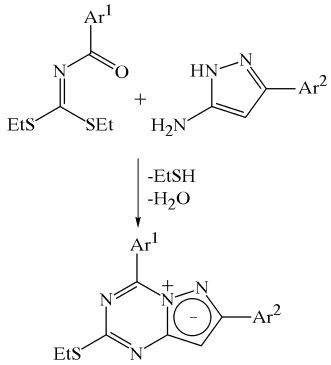
The molecular dimensions of 2-ethylsulfanyl-7-(4-methylphenyl)-4-phenylpyrazolo[1,5-*a*][1,3,5]triazine, $C_{20}H_{18}N_4S$, (I), 7-(4-chlorophenyl)-2-ethylsulfanyl-4-phenylpyrazolo[1,5-*a*][1,3,5]triazine, $C_{19}H_{15}ClN_4S$, (II), and 4,7-bis(4-chlorophenyl)-2-(ethylsulfanyl)pyrazolo[1,5-*a*][1,3,5]triazine, $C_{19}H_{14}Cl_2N_4S$, (III), show evidence for some aromatic delocalization in the pyrazole rings. The conformations adopted by the ethylsulfanyl substituents are different in all three compounds. There are no hydrogen bonds in any of the crystal structures, but pairs of molecules in (II) and (III) are linked into centrosymmetric dimers by π-stacking interactions.

Comment

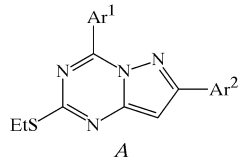
Compounds having a pyrazolo[1,5-*a*][1,3,5]triazine residue are of great interest in the treatment and prevention of central nervous system disorders (Bös *et al.*, 1999), metabolic and peripheral disorders (Darrow *et al.*, 2001), and Parkinson's and Alzheimer's diseases (Bös *et al.*, 1999). Recently, a pyrazolotriazine derivative has been reported to be a powerful corticotrophin releasing factor type 1 (CFR1) receptor antagonist (He *et al.*, 2000), playing an important role in modulating the endocrinal, autonomic and immune responses to stress (Kumar *et al.*, 2004).

Pyrazolo[1,5-*a*][1,3,5]triazines can be readily synthesized from 5-aminopyrazoles and an appropriate biselectrophilic reagent (Insuasty *et al.*, 2006). We report here the structure of three 4,7-diaryl-2-ethylsulfanylpyrazolo[1,5-*a*][1,3,5] triazines (Figs. 1–3), which were all obtained in good yields from the reactions of *S*,*S*-diethyl aroyliminodithiocarbonates with the appropriate 5-amino-3-arylpyrazoles (see scheme) using microwave irradiation under solvent-free conditions.

Compounds (I)–(III) are all very similar in composition and constitution, but they show some marked differences in both molecular conformation and crystal packing. Although analogous compounds containing 4-methylphenyl and 4-chlorophenyl substituents are often isomorphous and isostructural, no such similarities are apparent when compounds (I) and (II) are compared. These two compounds crystallize in



(I) $Ar^1=C_6H_5$; $Ar^2=C_6H_4CH_3$-4
(II) $Ar^1=C_6H_5$; $Ar^2=C_6H_4Cl$-4
(III) $Ar^1=Ar^2=C_6H_4Cl$-4



A

different crystal systems with markedly different cell dimensions; in addition, compound (I) exhibits orientational disorder in the unsubstituted phenyl ring, while compound (II) is fully ordered; furthermore, the structure of (II) contains a π–π stacking interaction which is absent from the structure of (I).

The bond distances within the heterocyclic portions of compounds (I)–(III) do not differ significantly from one compound to another (Table 1); however, the values themselves show some interesting features. In each compound, the

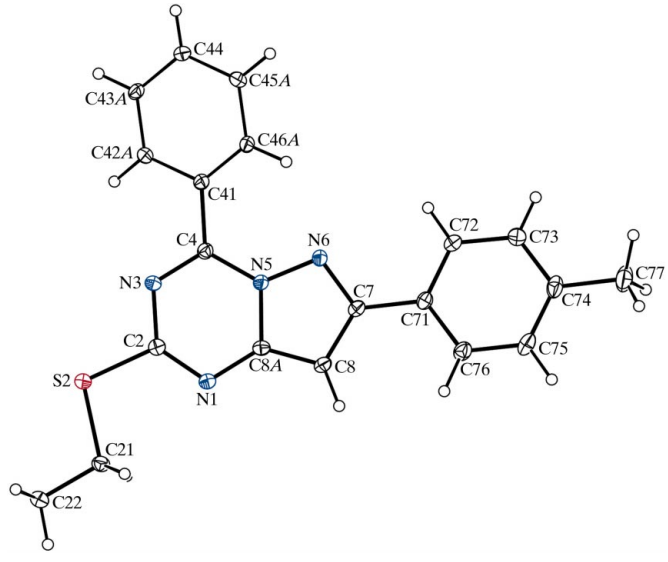


Figure 1
A molecule of (I), showing the atom-labelling scheme. For clarity, only one orientation of the disordered phenyl ring is shown. Displacement ellipsoids are drawn at the 30% probability level.

 DOI: 10.1107/S0108270107064074

N1—C2 and N3—C4 bonds are significantly shorter than any of the other C—N bonds, and the differences between the C7—C8 and C8—C8*A* bond distances [0.034 (4)–0.037 (4) Å] are much less than the difference (*ca* 0.15 Å) between typical single and double bonds of this type (Allen *et al.*, 1987). These observations are consistent with a measure of aromatic delocalization within the pyrazole ring, allied to strong bond fixation in the triazine ring, as opposed to the fully localized form *A* (see scheme). In compounds (I)–(III), the conformations of the ethylsulfanyl substituents are all different, as shown by the relevant torsion angles (Table 1); only in (I) are the non-H atoms of this substituent effectively coplanar with the adjacent triazine ring. The ring components in compounds (II) and (III) are almost coplanar, as shown by the dihedral angles (Table 1), but in compound (I) both of the aryl rings are displaced significantly further from the plane of the heterocyclic component than in either of (II) and (III).

There are no hydrogen bonds of any kind in the structures of compounds (I) and (II); however, in compounds (II) and (III), pairs of molecules are linked into centrosymmetric

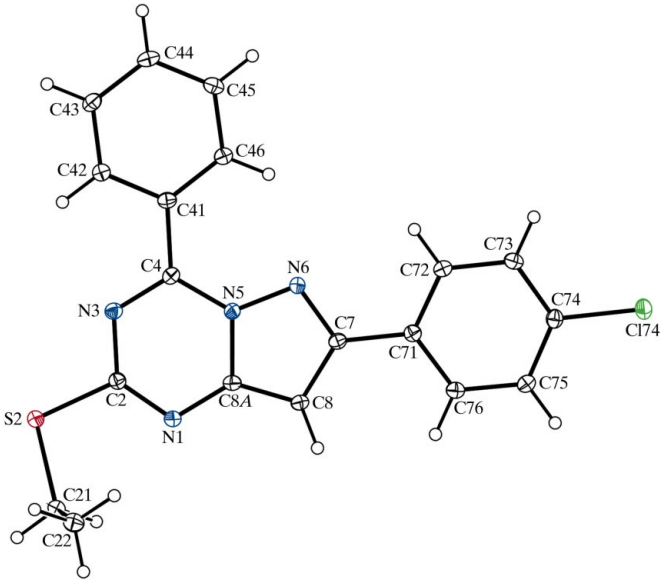


Figure 2
A molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

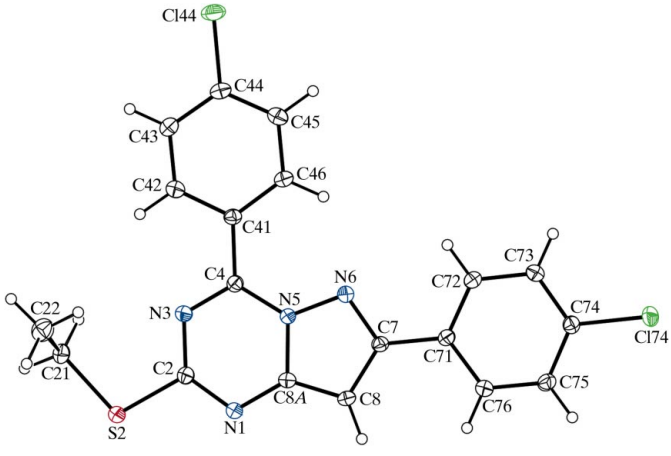


Figure 3
A molecule of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

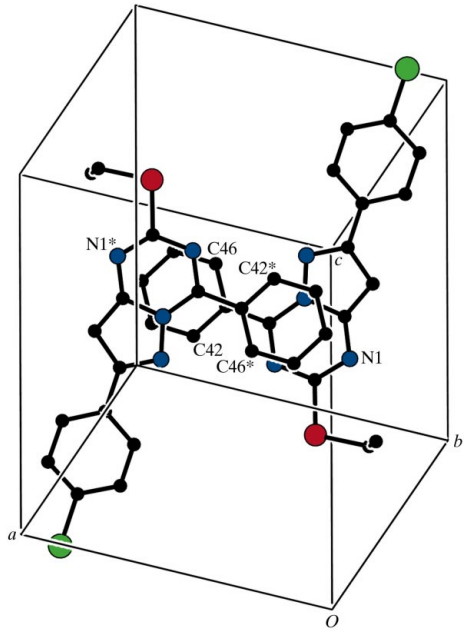


Figure 4
Part of the crystal structure of (II), showing the formation of a centrosymmetric π-stacked dimer. For clarity, H atoms have been omitted. Atoms marked with an asterisk (*) are at the symmetry position $(1 - x, 1 - y, 1 - z)$.

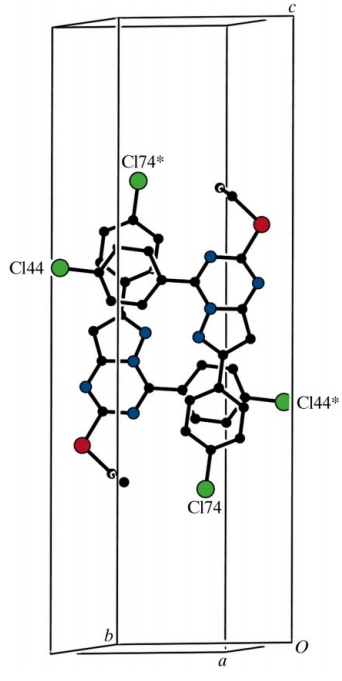


Figure 5
Part of the crystal structure of (III), showing the formation of a centrosymmetric π-stacked dimer. For clarity, H atoms have been omitted. Atoms marked with an asterisk (*) are at the symmetry position $(1 - x, 1 - y, 1 - z)$.

dimers by means of π–π stacking interactions. In compound (II), the triazine and unsubstituted phenyl rings in a pair of molecules related by inversion make a dihedral angle of 4.8 (2)°. The interplanar spacing is *ca* 3.39 Å, and the corresponding centroid separation is 3.551 (2) Å (Fig. 4). In compound (III), the two independent chlorophenyl rings of a centrosymmetrically related pair of molecules make a dihedral angle of 5.6 (2)°; here, the interplanar spacing is *ca* 3.53 Å, with a ring-centroid separation of 3.711 (2) Å (Fig. 5). In neither orientation of the molecule of compound (I) are there any stacking interactions.

Experimental

Equimolar quantities (2 mmol of each component) of an *S*,*S*-diethyl aroyliminodithiocarbonate and the appropriate 5-amino-3-arylpyrazole (see scheme) were placed in open Pyrex glass vessels and irradiated in a domestic microwave oven for 10–15 min to give the products (I)–(III). The compounds were purified by column chromatography on silica gel, using a mixture of hexanes and ethyl acetate (4:1 *v*/*v*) as eluant. After removal of the solvent, crystallization from ethyl acetate solutions provided crystals of (I)–(III) suitable for single-crystal X-ray diffraction [(I): yield 60%, m.p. 397 K; (II): yield 63%, m.p. 407 K; (III): yield 71%, m.p. 431 K].

Compound (I)

Crystal data

$C_{20}H_{18}N_4S$
M_r = 346.45
Triclinic, $P\overline{1}$
a = 4.8076 (3) Å
b = 11.6397 (5) Å
c = 15.5010 (7) Å
α = 92.164 (4)°
β = 96.217 (5)°
γ = 100.087 (4)°
V = 847.56 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.20 mm^{-1}
T = 120 (2) K
0.62 × 0.42 × 0.05 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.886, T_{max} = 0.990
13384 measured reflections
3861 independent reflections
2858 reflections with $I > 2\sigma(I)$
R_{int} = 0.036

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.106
S = 1.07
3861 reflections
264 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Compound (II)

Crystal data

$C_{19}H_{15}ClN_4S$
M_r = 366.86
Monoclinic, $P2_1/c$
a = 11.8290 (10) Å
b = 7.5703 (5) Å
c = 19.5297 (5) Å
β = 107.200 (3)°
V = 1670.61 (18) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.36 mm^{-1}
T = 120 (2) K
0.56 × 0.34 × 0.05 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.822, T_{max} = 0.982
37866 measured reflections
3822 independent reflections
2968 reflections with $I > 2\sigma(I)$
R_{int} = 0.039

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.092
S = 1.10
3822 reflections
227 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

Compound (III)

Crystal data

$C_{19}H_{14}Cl_2N_4S$
M_r = 401.30
Monoclinic, $P2_1/n$
a = 7.7117 (4) Å
b = 8.3261 (10) Å
c = 27.678 (3) Å
β = 94.978 (5)°
V = 1770.5 (3) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.50 mm^{-1}
T = 120 (2) K
0.47 × 0.24 × 0.14 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.801, T_{max} = 0.934
39992 measured reflections
4039 independent reflections
2513 reflections with $I > 2\sigma(I)$
R_{int} = 0.074

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.155
S = 1.06
4039 reflections
236 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.49 e Å^{-3}
$\Delta\rho_{min}$ = −0.50 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for compounds (I)–(III).

	(I)	(II)	(III)
N1—C2	1.309 (2)	1.305 (2)	1.318 (4)
C2—N3	1.368 (2)	1.364 (2)	1.358 (4)
N3—C4	1.312 (2)	1.314 (2)	1.310 (4)
C4—N5	1.368 (2)	1.374 (2)	1.366 (4)
N5—N6	1.366 (2)	1.3636 (19)	1.366 (3)
N6—C7	1.342 (2)	1.339 (2)	1.333 (4)
C7—C8	1.404 (3)	1.406 (2)	1.405 (4)
C8—C8*A*	1.367 (2)	1.370 (2)	1.371 (4)
C8*A*—N1	1.361 (2)	1.354 (2)	1.353 (4)
N5—C8*A*	1.402 (2)	1.399 (2)	1.403 (4)
N1—C2—S2—C21	−0.74 (16)	15.00 (16)	179.6 (2)
C2—S2—C21—C22	177.01 (12)	74.19 (14)	−80.3 (3)
Triazine/C41–C46	20.77 (13)/25.99 (13)[a]	4.78 (8)	7.58 (15)(9)
Pyrazole/C71–C76	10.20 (10)	2.63 (9)	2.52 (16)

Note: (*a*) values are given for both orientations of the disordered phenyl ring.

Crystals of (I) are triclinic; the space group $P\overline{1}$ was selected and confirmed by the structure analysis. For (II) and (III), the space groups $P2_1/c$ and $P2_1/n$, respectively, were uniquely assigned from the systematic absences. All H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions, with C—H distances of 0.95 (aromatic and heteroaromatic), 0.98 (CH_3) or 0.99 Å (CH_2), and with U_{iso}(H) = kU_{eq}(C), where k = 1.5 for the methyl groups and k = 1.2 for all other H atoms. In (I), the unsubstituted phenyl ring was found to exhibit orientational disorder; this was modelled using two sets of sites, labelled *A* and *B*, for atoms C42, C42, C45 and C46. Refinement of the site-occupancy factors for these two sets of atoms gave values that were identical within experimental uncertainly, and so these occupancies were fixed at 0.5 during the final refinements.

For all compounds, data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction:

EVALCCD (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

The authors thank Servicios Técnicos de Investigación of Universidad de Jaén and the staff for data collection. JC thanks the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain) and the Universidad de Jaén for financial support. HI, PM and GS thank COLCIENCIAS and Universidad de Nariño, Colombia, for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3133). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–19.

Bös, M., Riemer, C. & Stadler, H. (1999). EU Patent 941 994 A1.

Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. & Spagna, R. (2005). *J. Appl. Cryst.* **38**, 381–388.

Darrow, J. W., Lombaert, S., Blum, C., Tran, J., Giangiordano, M., Griffith, D. A. & Carpino, P. A. (2001). WO Patent 023388 A2.

Duisenberg, A. J. M., Hooft, R. W. W., Schreurs, A. M. M. & Kroon, J. (2000). *J. Appl. Cryst.* **33**, 893–898.

Duisenberg, A. J. M., Kroon-Batenburg, L. M. J. & Schreurs, A. M. M. (2003). *J. Appl. Cryst.* **36**, 220–229.

Ferguson, G. (1999). *PRPKAPPA*. University of Guelph, Canada.

He, L., Gilligan, P. J., Zaczek, R., Fitzgerald, L. W., McElroy, J., Shen, H.-S. L., Saye, J. A., Kalin, N. H., Shelton, S., Christ, D., Trainor, G. & Hartig, P. (2000). *J. Med. Chem.* **43**, 449–456.

Hooft, R. W. W. (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.

Insuasty, H., Estrada, M., Cortés, E., Quiroga, J., Insuasty, B., Abonía, R., Nogueras, M. & Cobo, J. (2006). *Tetrahedron Lett.* **47**, 5441–5443.

Kumar, J. S. D., Majo, V. J., Simpson, N. R., Prabhakaran, J., Van Heertum, R. L. & Mann, J. J. (2004). *J. Labelled Compd Radiopharm.* **47**, 971–976.

McArdle, P. (2003). *OSCAIL for Windows*. Version 10. Crystallography Centre, Chemistry Department, NUI Galway, Ireland.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Sheldrick, G. M. (2003). *SADABS*. Version 2.10. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.