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ORIGINAL PAPER

The X-ray Structures of 2,4-Dibromothiazole and 2,4-Diacetyl-5-bromothiazole

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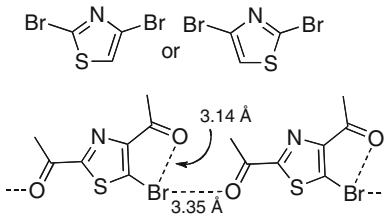
Abstract 2,4-Dibromothiazole [orthorhombic, a = 6.700 (10), b = 16.21 (3), c = 5.516 (8) Å, space group Fmm2] shows a disordered crystal structure with molecules randomly oriented with respect to the direction of the Br–C(2)–N–C(2)–Br unit and the remaining ring atoms S(3) and C(3)H showing mixed occupancy. 2,4-Diacetyl-5-bromothiazole [triclinic, a = 4.040 (2), b = 8.254 (5), c = 13.208 (8) Å, α = 96.191 (17), β = 93.865 (16), γ = 94.067 (11)°, space group P-1] shows a structure dominated by halogen bonding, intramolecular between 4-COMe and 5-Br and intermolecular between 2-COMe of one molecule and 5-Br of the next.

Graphical Abstract 2,4-Dibromothiazole is disordered in the crystal structure with molecules randomly oriented either way round as shown. There is evidence for unusual intramolecular, and perhaps also intermolecular, halogen bonding between Br and C = O in the structure of 2,4-diacetyl-5-bromothiazole.



Keywords Thiazole · Bromothiazole · Disorder · Halogen bonding

Introduction

Some time ago we reported the synthesis of 2,4-diacetylthiazole **1**, a compound of interest for its flavour and aroma properties, by bromination of diethylthiazole **2** to give **3** followed by treatment with silver nitrate in aqueous ethanol (Scheme 1) [1]. In the course of this work, several new brominated thiazole derivatives were obtained, and we present here the X-ray structure determination of two of these of particular interest: 2,4-dibromothiazole **4** and 2,4-diacetyl-5-bromothiazole **6**. Compound **4** was prepared as a potential alternative precursor to **1** using lithium/halogen exchange followed by acetylation with *N*-acetylmorpholine [2], but in agreement with the literature reports, even with two or more equivalents of reagents under a variety of conditions, this proceeded only once on the 2-position and the 4-positon was unreactive. The traditional synthesis of **4** requires treatment of the commercially available thiazolidine-2,4-dione **5** with a large excess of expensive $POBr_3$ but we obtained it using the recently reported improved synthesis involving reaction of **5** with P_2O_5 and Bu_4NBr in toluene [3]. In our reported synthesis of **1** [1], the

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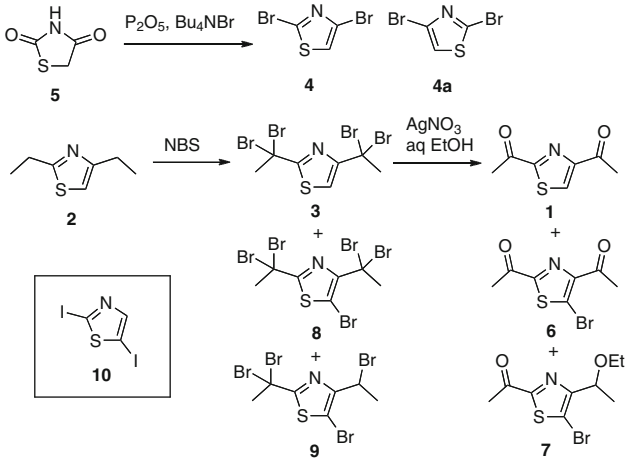

Scheme 1 Synthetic routes used to compounds **1**, **4**, **6** and **7** and structure of **10**

bromination of **2** gave a range of other byproducts besides the desired tetrabromide **3**. Treating the mixture with silver nitrate in aqueous ethanol gave mainly **1** and, as the most volatile component present, this was separated in pure form by vacuum distillation, but in only 49 % yield. If the crude mixture was instead subjected to column chromatography it allowed isolation of compounds **6** and **7**, respectively derived from **8** and **9**. There is therefore a competition between bromination at the 4-ethyl group and ring bromination at position 5 in **2** resulting in the observed mixture of three products. Compound **7** was obtained after distillation as a colourless liquid while compound **6** was recrystallised from hexane to afford a sample suitable for X-ray diffraction.

Experimental

2,4-Dibromothiazole 4

This compound was prepared by reaction of commercially available thiazolidine-2,4-dione **5** with P_2O_5 and Bu_4NBr in boiling toluene [3]. It was obtained directly as colourless crystals suitable for X-ray diffraction which gave the following data: mp 81–82 °C (81.1–82.4 °C [3]; ^{1}H NMR ($CDCl_3$) δ 7.21 (1H, s); ^{13}C NMR δ 120.8 (CH), 124.3 (C-4) and 136.3 (C-2).

2,4-Diacetyl-5-bromothiazole 6 and 2-Acetyl-5-bromo-4-(1-ethoxyethyl)thiazole 7

A solution of the mixture of products from NBS bromination of 2,4-diethylthiazole **2** (60.55 g, 131.4 mmol) in ethanol (500 cm^3) was mixed with a solution of silver nitrate (111.6 g, 657 mmol) in water (170 cm^3) and the mixture was heated under reflux for 20 min. It was cooled and acidified with 12 M hydrochloric acid (190 cm^3). The solid silver salts were filtered off and the filtrate was evaporated down to 150 cm^3, neutralised with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 50 cm^3). The extracts were dried ($MgSO_4$) and evaporated and the residue was subjected to column chromatography (SiO_2, Et_2O/hexane, 1:1). Three fractions were obtained:

2-Acetyl-5-bromo-4-(1-ethoxyethyl)thiazole 7

4.31 g (12 %) as a colourless liquid, bp 158–160 °C (oven temp)/3 Torr. ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, *J* 7), 1.57 (3H, d, *J* 7), 2.69 (3 H, s), 3.39 and 3.49 (2H, AB pattern of q, *J* 9, 7) and 4.78 (1 H, q, *J* 7), ^{13}C NMR ($CDCl_3$) δ 15.3 (CH_2*Me*), 20.4 (*Me*CHOEt), 25.4 (MeCO), 64.5 (C*H*OEt), 71.1 (OCH_2), 115.0 (C-5), 157.8 (C-4), 166.9 (C-2) and 191.2 (CO); HRMS *m/z* found: 299.9668. $C_9H_{12}^{79}BrNaNO_2S$ (*M* + Na) requires 299.9670; found: 301.9641. $C_9H_{12}^{81}BrNaNO_2S$ (*M* + Na) requires 301.9649.

2,4-Diacetyl-5-bromothiazole 6

1.80 g (5.5 %) as colourless crystals, mp 83–84 °C; (Found: C, 33.9; H, 2.0; N, 5.3. $C_7H_6BrNO_2S$ requires C, 33.9; H, 2.4; N, 5.6 %); ^{1}H NMR ($CDCl_3$) δ 2.708 (3H, s, 2-CO*Me*) and 2.724 (3H, s, 4-CO*Me*); ^{13}C NMR ($CDCl_3$) δ 25.1 (2-CO*Me*), 28.7 (4-CO*Me*), 122.7 (C-5), 150.1 (C-4), 165.2 (C-2), 190.6 (CO, 2-*CO*Me), 192.6 (CO, 4-*CO*Me) [assignment of ^{1}H and ^{13}C NMR signals supported by HMBC study]; HRMS *m/z* found: 269.9191. $C_7H_6^{79}BrNNaO_2S$ (*M* + Na) requires 269.9200; found: 271.9185. $C_7H_6^{81}BrNNaO_2S$ (*M* + Na) requires 271.9180.

2,4-diacetylthiazole 1

12.6 g (57 %) as colourless crystals, mp 65–68 °C, data as reported in [1].

Data were collected using a Rigaku MM007 RA and a Mercury CCD (confocal optics Mo-Kα radiation) at 93 K. Intensity data were collected using ω/ϕ steps accumulating area detector frames spanning at least a hemisphere of reciprocal space (data were integrated using CrystalClear). All data were corrected for Lorentz, polarisation and long-term intensity fluctuations. Absorption effects were corrected on the basis of multiple equivalent reflections. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). Hydrogen atoms were assigned riding isotropic displacement parameters and constrained to idealised geometries. Table 1 summarises the X-ray data.

Table 1 Crystal data and structure refinement details for **4** and **6**

	4	**6**
CCDC deposit no.	1033511	1033512
Empirical formula	C_3HBr_2NS	$C_7H_6BrNO_2S$
Formula weight	242.92	248.09
Crystal system	Orthorhombic	Triclinic
Space group	Fmm2	P-1
Temperature (K)	93(2)	93(2)
Crystal form	Colourless prism	Colourless prism
	0.10 × 0.02 × 0.02 mm	0.15 × 0.15 × 0.15 mm
Unit cell dimensions	$a = 6.700$ (10) Å	$a = 4.040$ (2) Å
	$b = 16.21$ (3) Å	$b = 8.254$ (5) Å
	$c = 5.516$ (8) Å	$c = 13.208$ (8) Å
		$\alpha = 96.191$ (17)°
		$\beta = 93.865$ (16)°
		$\gamma = 94.067$ (11)°
Volume (Å^3)	599.0 (16)	435.5 (4)
Z	4	2
D_c (g cm^{-3})	2.694	1.892
Absorption coefficient	13.79 mm^{-1}	4.928 mm^{-1}
Radiation type, wavelength	Mo $K\alpha$, 0.71073 Å	Mo $K\alpha$, 0.71073 Å
$F_{(000)}$	448	244
θ ραννγε	2.51–25.35°	2.50–27.50°
Limiting indices	$-7 \le h \le 7$, $-19 \le k \le 14$,	$-4 \le h \le 4$, $-9 \le k \le 9$,
	$-6 \le l \le 6$	$-15 \le l \le 15$
Reflections collected/unique	874/308	6521/1573
R_{int}	0.1615	0.0978
Data/restraints/parameters	308/14/29	1573/0/111
Data with $I > 2\sigma(I)$)	278	1355
Goodness of fit on F^2	1.110	0.925
R_1, wR_2 (data with $I > 2\sigma(I)$)	0.0940, 0.2337	0.0543, 0.1367
R_1, wR_2 (all data)	0.1011, 0.2545	0.0564, 0.1374
Largest diff. peak/hole (e Å^{-3})	1.030 and −1.729	1.944 and −1.351
Flack parameter	0.00 (9)	–

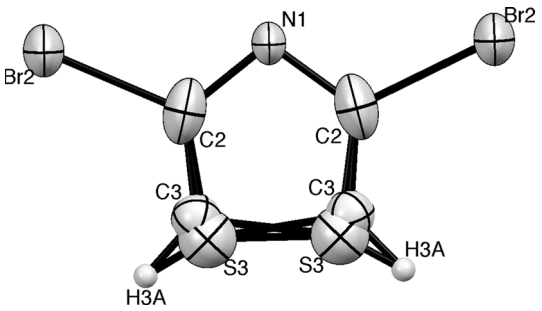

Fig. 1 The molecular structure of **4** showing numbering system used

Table 2 Bond lengths and angles for **4**

Bond	Length (Å)	Atoms	Angle (°)
Br(2)–C(2)	1.91 (5)	Br(2)–C(2)–N(1)	118 (4)
C(2)–N(1)	1.35 (6)	C(2)–N(1)–C(2)	105 (5)
C(2)–C(3)	1.35 (2)	Br(2)–C(2)–S(3)	123 (2)
C(3)–S(3)	1.8 (1)	N(1)–C(2)–S(3)	119 (4)
S(3)–C(2)	1.61 (5)	C(2)–S(3)–C(3)	91 (3)
		S(2)–C(3)–C(2)	103 (4)
		C(3)–C(2)–N(1)	123 (5)
		C(3)–C(2)–Br(2)	120 (3)

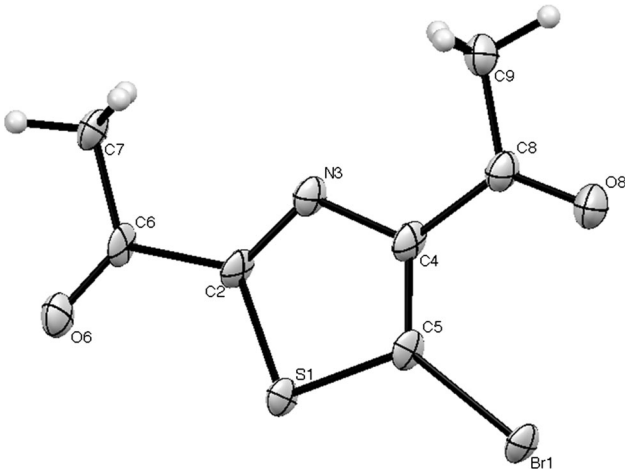

Fig. 2 The molecular structure of **6** showing numbering system used

Table 3 Bond lengths, angles and torsion angles for **6**

Bond	Length/Å	Atoms	Angle/°
C(2)–S(1)	1.729 (6)	S(1)–C(2)–C(3)	115.8 (4)
S(1)–C(5))	1.710 (5)	C(2)–N(3)–C(4)	111.0 (4)
C(5)–C(4)	1.382 (8)	N(3)–C(4)–C(5)	113.3 (5)
C(4)–N(3)	1.383 (7)	C(4)–C(5)–S(1)	111.5 (4)
N(3)–C(2)	1.301 (7)	C(5)–S(1)–C(2)	88.4 (3)
C(5)–Br(1)	1.864 (5)		
C(4)–C(8)	1.481 (8)	N(3)–C(4)–C(8)–O(8)	179.0 (5)
C(8)–O(8)	1.206 (7)	N(3)–C(2)–C(6)–O(6)	176.4 (5)
C(8)-C(9)	1.501 (8)		
C(2)–C(6)	1.495 (8)		
C(6)–O(6)	1.204 (7)		
C(6)–C(7)	1.502 (8)		

Results and Discussion

The molecular structure of **4** is shown in Fig. 1. As expected it is perfectly planar, but is disordered with respect to the orientation of the molecule, with forms **4** and **4a** having a sufficiently similar overall shape, dominated by the large bromine atoms, to fit equally well into the lattice. The bond lengths and angles (Table 2) obtained for the Br–C–N–C–Br section of the molecule are therefore mean values for the hybrid between structures **4** and **4a**. There have been few previous structural studies on simple halogenated thiazoles, and among all the possible mono-, di- and trihalothiazoles the only one to be previously characterised by X-ray diffraction is 2,5-diiodothiazole **10** [4]. Although one could envisage a similar disorder with the I–C–S–C–I unit randomly arranged and mixed occupancy of N and 4-CH, no such phenomenon occurs in that case.

When we come to the structure of compound **6** (Fig. 2; Table 3), the whole molecule including the two acetyl groups is essentially planar. There is some evidence for both intra- and intermolecular halogen bonding between the C–Br and the C(4)–acetyl of the same molecule and the C(2)–acetyl of the next molecule. The pattern is shown in Fig. 3 and the parameters are given in Table 4. Halogen bonding in general has been of considerable recent interest [5–8] and such an interaction between bromine and carbonyl oxygen has been studied both computationally [9, 10] and experimentally [11] in simple molecules, and by surveying complex biological structures [12]. However the two interactions here show unusual features. The intramolecular interaction with O(8) results in a definite

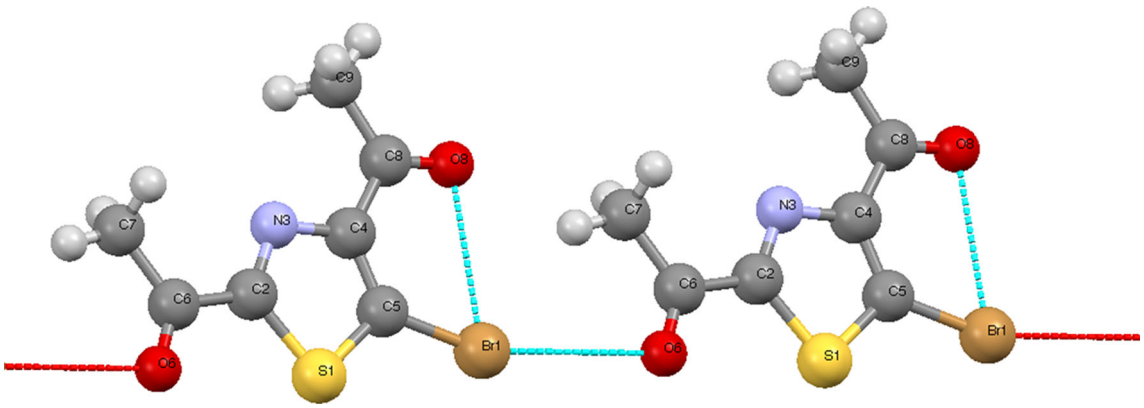

Fig. 3 Halogen bonding pattern in the crystal structure of **6** viewed along the *a* axis

Table 4 Geometric parameters for intra and intermolecular halogen bonding in **6**

D–Br···O = A	d (D–Br)	d (Br···O)	<(DBrO)	<(BrOA)
C(5)–Br(1)···O(8) = C(8)	1.864 (5)	3.140 (5)	67.0 (2)	95.2 (3)
C(5)–Br(1)···O(6) = C(6)	1.864 (5)	3.352 (5)	160.0 (2)	112.8 (3)

shortening of the interatomic distance compared to the sum of van der Waals radii (ca. 3.37 Å [12] or 3.35 Å [13]) but the angles involved, both at bromine and oxygen, are far from the normally accepted optimal range. On the other hand the intermolecular interaction with O(6) results in a very marginal shortening in interatomic distance compared to the sum of van der Waals radii, despite the angles being much more favourable.

Conclusion

Both the simple bromothiazole structures reported here display unexpected features. The disordered structure of **4** obviously arises from the relatively small difference in the size of S versus CH when compared to the dominant large bromine atoms. The structure of **6** shows some evidence of halogen bonding but this is highly unusual. Paradoxically the intramolecular interaction, which seems clear based on the interatomic distances, involves unprecedented and almost impossible angles, while the intermolecular interaction, for which the angles are almost ideal, is so weak as to be almost insignificant. Further structural studies of simple halogenated heterocycles are clearly required to fully understand the forces at work.

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