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The synthesis of bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfides and other related 1,3,4-oxadiazoles from 1,1′-diphenylthiodiacetic acid dihydrazide and triethyl *ortho*esters

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ABSTRACT

Reactions of symmetrical 1,1′-diphenylthiodiacetic acid dihydrazide and triethyl *ortho*esters in the presence of catalytic amount of glacial acetic acid resulted in the formation of three heterocyclic products: the appropriate bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfides, 2-benzyl-1,3,4-oxadiazoles and 2-benzoyl-1,3,4-oxadiazoles. The presence of the latter two compounds is connected with carbon–sulfur fission in the molecule of the starting hydrazide. The identity of the unexpected fission products was confirmed by parallel syntheses of the model 1,3,4-oxadiazoles from phenylacetic acid hydrazide and 2-hydroxymethyl-1,3,4-oxadiazole derivatives.

1. Introduction

Carboxylic acid hydrazides constitute useful precursors for the synthesis of nitrogen- and nitrogen–oxygen containing heterocycles. Numerous transformations of this class of compounds are known to lead to four-membered azetidines,[1,2] five-membered pyrroles,[3,4] 1,3,4-oxadiazoles[5–9] or 1,2,4-triazoles[10,11] and to six-membered systems, such as substituted pyrimidines,[12] oxadiazines[13] or triazines.[14–16] However, the arrangements possessing an additional reactive group at the α position seem to be the more powerful tools in diverse synthetic strategies than the unsubstituted hydrazides. Our earlier studies on the reactions of some α-hydroxycarboxylic acid hydrazides and triethyl *ortho*esters have proved this assumption and led us to both acyclic and heterocyclic products. In the group of acyclic compounds, the appropriate *N*-ethoxymethylene hydrazides or the more extended *N*,*N*′-bis(methanecarbonylamino)formamidines were synthesised in neutral media.[17] They underwent further cyclisation in acidic medium to 4-acylamino-1,2,4-triazoles,[17] 2-hydroxymethyl-1,3,4-oxadiazoles and 1,3,4-oxadiazin-5(6*H*)-ones.[18] The formation of six-membered 1,2,4-triazin-6(5*H*)-ones and five-membered 2-aminomethyl-1,3,4-oxadiazoles has also been observed in the reactions of hydrazides of free α-aminocarboxylic acid and *ortho*esters.[19] The protection of the highly reactive amino group increased the selectivity of the transformation and led to one type of product, the derivatives of 1,3,4-oxadiazole.[20] This class of five-membered aromatic heterocycles is of particular interest for medicinal chemistry because many 1,3,4-oxadiazole derivatives exhibit strong antibacterial, anticonvulsant and anticancer activities.[21–23] They are also applied in agriculture as pesticides[24,25] or in polymer and material science in the production of organic light-emitting diodes (OLEDs) and optical brighteners.[26,27] A wide range of synthetic procedures employing the mentioned carboxylic acid hydrazides,[5–9] *N*,*N*′-diacylhydrazines[28–31] or 1,2,4-oxadiazoles[32,33] (as the synthons of 1,3,4-oxadiazole motif) has been described in literature.

In continuation of our studies on the application of acid hydrazides as potent reagents in the synthesis of heterocyclic rings, we investigated structures possessing a sulfur-containing reactive group in the α position. Herein, we report the synthesis of 1,1′-diphenylthiodiacetic acid dihydrazide and its reactions with triethyl *ortho*esters.

2. Results and discussion

The key compound in the synthesis of the sulfur-containing 1,3,4-oxadiazoles was the dihydrazide of 1,1′-diphenyl-2,2′-

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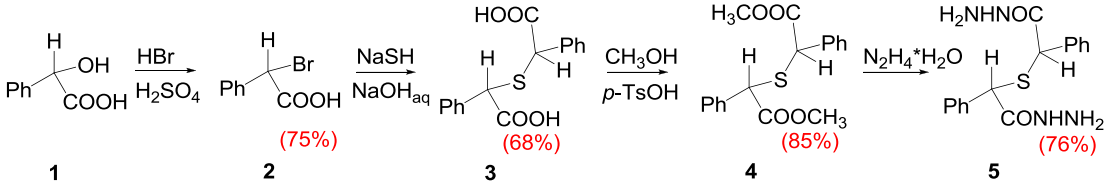
thiodiacetic acid **5**. This molecule was obtained from racemic DL-mandelic acid according to a short procedure (Scheme 1).



Scheme 1. Synthesis of 1,1′-diphenylthiodiacetic acid dihydrazide.

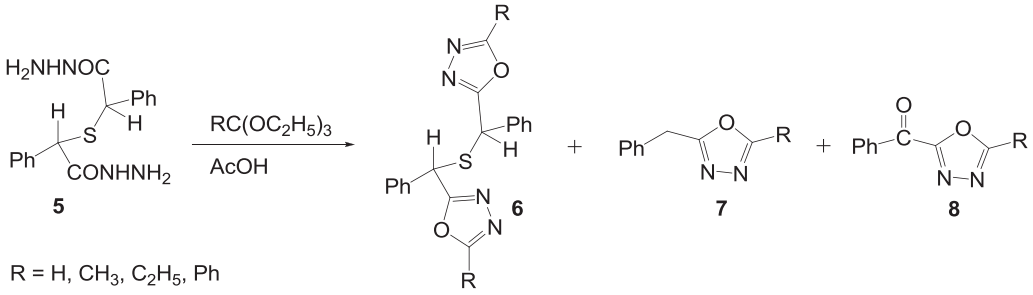
First, acid **1** was treated with HBr in the presence of sulfuric acid yielding the substitution product, α-bromophenylacetic acid **2**.[34] The heating of α-bromophenylacetic acid **2** with sodium hydrosulfide NaSH in a basic solution resulted in the formation of the disubstituted product,[35] the appropriate 1,1′-diphenylthiodiacetic acid **3**. The acid was then esterified with methanol in the presence of *p*-TsOH and treated with hydrazine hydrate to form the dihydrazide of 1,1′-diphenylthiodiacetic acid **5** in satisfactory yields. The structure of this crystalline, high-melting product was confirmed by elemental analysis and typical spectroscopic methods.

Hydrazide **5** was heated with an excess of triethyl *ortho*esters (R=H, CH_3, C_2H_5, Ph, Scheme 2) in the presence of catalytic amounts of glacial acetic acid. The reaction was conducted until the starting hydrazide was fully consumed, as monitored by TLC. Heating for a few hours predominantly afforded the expected bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfides **6**. Contrary to the previously examined reactions of α-hydroxy- and α-amino-carboxylic acid hydrazides with *ortho*esters,[18–20] the highest yields here were obtained in the case of the unsubstituted arrangement **6a** and its derivatives, **6b** and **6c**, which were substituted with alkyl groups at position 5 (65–80%, Table 1). Surprisingly, two other compounds from the 1,3,4-oxadiazole family were also found in the reaction mixture. These molecules were identified as 2-benzyl-1,3,4-oxadiazoles **7**, whose yields increased with the bulk of the substituent in the *ortho*ester molecule, and 2-benzoyl-1,3,4-oxadiazoles **8**.

additional synthetic procedures were indeed necessary. At first, we focused on the synthesis of 2-benzyl-1,3,4-oxadiazoles **7a**–**d**. A reaction similar to that of the hydrazide of phenylacetic acid **9** and triethyl *ortho*esters was applied to produce the model derivatives (Scheme 4). The reaction, held again in the presence of AcOH, gave the desired 5-substituted 2-benzyl-1,3,4-oxadiazoles in high yields (62–85%, Table 2).

Another group of the model 2-benzoyl-1,3,4-oxadiazoles **8** was obtained by oxidation of the appropriate 2-(1-hydroxy-1-phenylmethyl)-1,3,4-oxadiazoles **11** (Scheme 4), which were produced earlier in the reaction between the hydrazide of mandelic acid and triethyl *ortho*esters.[18] The transformation was performed in a two-phase system at room temperature with the use of a $K_2Cr_2O_7$/H_2SO_4 mixture.[42] The products, ketones **8**, were easily obtained in high yields as stable solids with low melting temperatures. Similar to the previously analysed **7a**–**d**, the highest yields were observed in the case of the conjugated system **8d** (88%, Table 2).

The structures of products obtained in the reactions of 1,1′-diphenylthiodiacetic acid dihydrazide **5** with triethyl *ortho*esters (**6a**–**d**, **7a**–**d**, **8a**–**d**) were confirmed with elemental analyses and typical spectroscopic methods (^{1}H and ^{13}C NMR, UV, MS, IR). In the ^{1}H NMR spectra of bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfides **6**, one can observe the reduced number of proton signals due to the fact, that compounds like these possess a symmetrical structure. The most characteristic peak is associated with the proton adjacent to carbon at the α position to the bridging sulfur atom, which appears as a singlet in the range from 5.39 to 5.83 ppm. The carbon atom mentioned above is seen in the ^{13}C NMR spectra at approximately 44 ppm. In the series of simple 2-benzyl-1,3,4-oxadiazoles **7**, the diagnostic signal in the ^{1}H NMR spectra is the singlet associated with the two protons of the methylene group, which is observed in the range between 4.13 and 4.34 ppm. The characteristic carbon



Scheme 2. The reaction of 1,1′-diphenylthiodiacetic acid dihydrazide (**5**) with triethyl *ortho*esters.

Table 1
Products of the reaction of 1,1′-diphenylthiodiacetic acid dihydrazide with triethyl *ortho*esters in the presence of catalytic amounts of AcOH

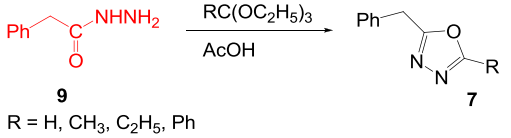
Entry	R	Reaction time [h]	Reaction temperature [° C]	Product **6**	Product **7**	Product **8**
				Yield [%]	Yield [%]	Yield [%]
a	H	15	145	80	10	8
b	CH_3	10	142	70	18	10
c	C_2H_5	10	152	65	20	10
d	Ph	5	240	30	49	15

To confirm the structure of the unexpected 1,3,4-oxadiazoles **7a**–**d** and **8a**–**d**, authentic samples were synthesised. In fact, some of these molecules have been described in literature (Table 2); however, due to the lack of their spectroscopic and physical data, the

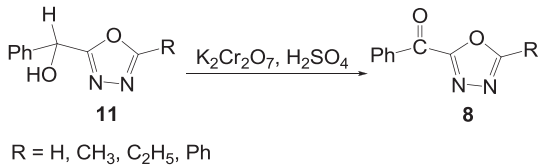
Table 2
Products of the parallel syntheses of the model 5-substituted 2-benzyl-1,3,4-oxadiazoles[a] (**7a**–**d**, Scheme 3) and 2-benzoyl-1,3,4-oxadiazoles[b] (**8a**–**d**, Scheme 4)

Entry	R	Product **7**				Product **8**		
		Reaction time [h]	Reaction temperature [° C]	Yield [%]	Ref.	Reaction time [h]	Yield [%]	Ref.
a	H	13	145	62	36	2	78	—
b	CH_3	10	142	77	37	2	75	40
c	C_2H_5	10	152	75	38	2	82	—
d	Ph	5	240	85	39	2	88	41

[a] The reaction was conducted in excess of *ortho*ester and in the presence of AcOH (reflux).
[b] The oxidation was performed in an ether/benzene solution with the use of a $K_2Cr_2O_7/H_2SO_4$ mixture (rt).



Scheme 3. The parallel synthesis of the model 5-substituted 2-benzyl-1,3,4-oxadiazoles (**7a**–**d**).



Scheme 4. The parallel synthesis of the model 5-substituted 2-benzoyl-1,3,4-oxadiazoles (**8a**–**d**).

atom appears in the ^{13}C NMR spectra at approximately 31 ppm. In terms of the derivatives of 2-benzoyl-1,3,4-oxadiazole **8**, the carbonyl carbon atom, observed in the ^{13}C NMR spectra at ~177 ppm, is the diagnostic signal. Interestingly, analysing the spectra of 1,3,4-oxadiazoles substituted with the phenyl group at position 5, one should focus on the characteristic phenyl H2′ and H6′ proton shifts. These two protons of **6d**, **7d** and **8d** are shifted in the ^1H NMR spectra to low fields and appear as a doublet between 7.94 and 8.12 ppm. Such significant changes in the chemical shifts could result from the proximity of the H2′ and H6′ protons to the ring's nitrogen and oxygen atoms or from the presence of hydrogen bonds linking heteroatoms and the indicated protons.

To establish the structure of derivatives **6**, X-ray analysis was also performed. The molecular structure of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide **6c**, with the atomic numbering scheme, is shown in Fig. 1.

The X-ray analysis of **6c** confirmed the symmetrical structure of the molecule possessing the centre of symmetry at the sulfur atom. The absolute configuration in the crystal at both C2 and C2′ atoms is identical and identified as (*R*,*R*), which means that optically inactive **6c** is in fact the racemic mixture of (*R*,*R*) and (*S*,*S*) enantiomers. The molecular packing in the crystal is influenced by the presence of weak intramolecular C—H···O hydrogen bond connecting the hydrogen atom adjacent to C13 carbon atom of the phenyl group with O4 oxygen atom of the heterocyclic ring. The C···O distance is 2.958(3) Å while the C—H···O angle is 111.00°. The plane of the benzene ring makes the angle of 39.31° with the plane of the heterocyclic ring. In the crystal structure of **6c**, molecules are linked by one weak C—H···N hydrogen bond: C2—H···N7(*i*) (*i*=−*x*, *y*, 0.5−*z*) with C···N distance of 3.352(3) Å and C—H···N angle of 137.00°.

The presence of the two unexpected reaction products **7** and **8** encouraged us to the further study the possible reaction mechanism. Generally, sulfides R^1—S—R^2 are stable compounds in both acidic and basic media. However, extended arrangements with an electron-withdrawing phenyl group and hydrogen atom at the α-carbon atom, can easily undergo alkaline fission via to two different mechanisms. The first approach by Teich and Curtin,[43]

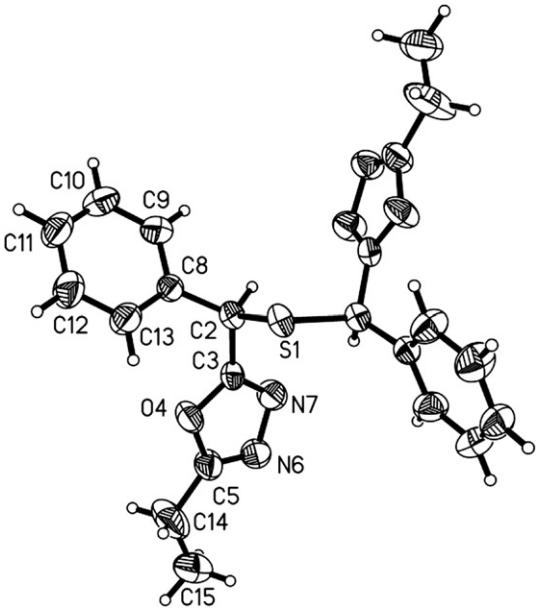
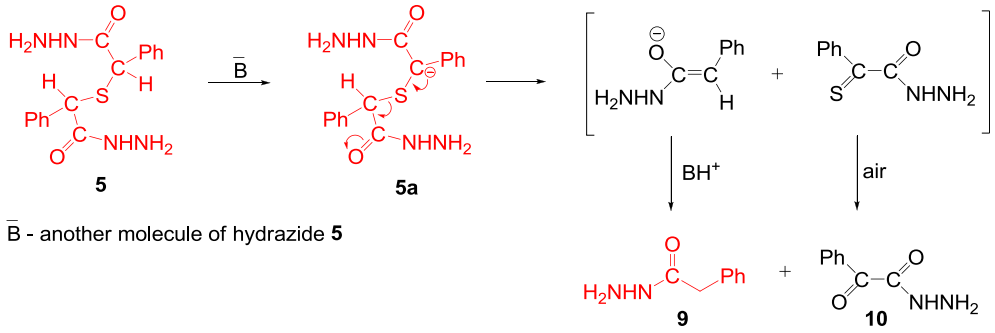


Fig. 1. The molecular structure of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide **6c** showing the atom-labelling scheme. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

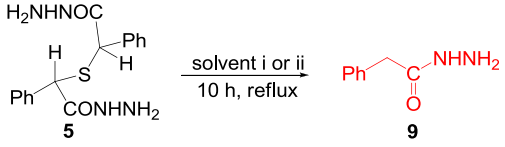
proposed for (α-benzoylmethylthio)acetic acid derivatives, involves proton abstraction caused by a hydroxyl ion and the subsequent C—S bond dissociation (path a). In the second approach, the hydroxyl ion add to the sulfur atom, causing the separation of the C—S bond in the resulting anion (path b).[44] Nevertheless, the products of the fission are the same in both cases.

Analysing the mechanism, we concluded that the dihydrazide of 1,1′-diphenyl-2,2′-thiodiacetic acid **5** undergoes decomposition in boiling *ortho*ester according to path a, where the hydrazide (Scheme 5), possessing a basic terminal —$NHNH_2$ group, abstracts the proton from the α-carbon atom, relative to the bridging —S— atom. The alternative mechanism that involves the addition of another hydrazide molecule seems less probable due to steric hindrance. The fission of anion **5a** leads to the formation of a less crowded ion, which abstracts a proton from the protonated hydrazide molecule BH^+ and transforms into the appropriate benzyl derivative **9**. The thermally unstable sulfur-containing derivative, that is, simultaneously formed is converted into dicarbonyl compound **10** (Scheme 5) under the influence of air with sulfur liberation.[43] A similar side reaction was observed earlier by Hartnedy and Dittmer for monothiobenzil.[45] Indeed, the study of the ^{13}C NMR spectra of the reaction products **8a**–**d** showed a lack of the thiocarbonyl group C=S but the presence of the additional carbonyl group C=O. However, analysing the reaction of 1,1′-diphenylthiodiacetic acid dihydrazide **5** with triethyl *ortho*esters (Scheme 2), one could suppose that two simple products **7** and **8** may also arise from bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide **6**. The heating of the considered sulfides **6** in the excess of the appropriate triethyl *ortho*ester and in the presence of catalytic



Scheme 5. The proposed mechanism of the carbon–sulfur fission.

amounts of glacial acetic acid revealed that these compounds are stable in such conditions. Consequently, the main reaction between symmetrical 1,1′-diphenylthiodiacetic acid dihydrazide **5** and triethyl *ortho*esters was accompanied by the fission of the starting material **5** and resulted in the formation of two other hydrazides, **9** and **10**; these two side products readily reacted with the *ortho*esters to yield the appropriate 1,3,4-oxadiazole derivatives. One should notice the high yield of 2-benzyl-5-phenyl-1,3,4-oxadiazole **7d** (49%, Table 1) in contrast to the other compounds of this group. However, we must remember that the reactions were conducted with the excess of the *ortho*ester because it played the dual role of the reagent, introducing the methylene group into the product, and the solvent. The large difference exists in the boiling points of triethyl *ortho*benzoate (bp 240 °C) and the rest of the *ortho*esters (bp 142–152 °C), which may explain why the most effective hydrazide fission occurred at high temperatures. To confirm our hypothesis, hydrazide **5** was heated under reflux for 10 h in two different solvents: anisole (bp 154 °C) and 2-phenoxyethanol (bp 237 °C). The reaction mixture was separated by column chromatography, and the content of phenylacetic acid hydrazide **9** was estimated (Scheme 6).



Scheme 6. The fission of **6** by heating in different solvents: (i) anisole; (ii) 2-phenoxyethanol.

The fission of 1,1′-diphenylthiodiacetic acid dihydrazide **5** was observed in both solvents. However, the highest yield of phenylacetic acid hydrazide **9** was achieved in the case of high-boiling 2-phenoxyethanol (35%, see Experimental section). The experiment confirmed the influence of temperature on the course of this side reaction and let us explain the question of the increased yield of 2-benzyl-5-phenyl-1,3,4-oxadiazole **7d** in the entire reaction series.

3. Conclusions

The reported procedure offers a facile and effective way to obtain symmetrically substituted bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfides. The starting 1,1′-diphenylthiodiacetic acid dihydrazide undergoes carbon–sulfur fission at elevated temperatures, which leads to the formation of two other simple hydrazides. These additional hydrazides are the real sources of the different related 1,3,4-oxadiazoles produced in the reactions with triethyl *ortho*esters.

4. Experimental

4.1. General

Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were performed with a VarioEL analyser in PAN Zabrze. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 spectrometer in DMSO or $CDCl_3$ solutions using TMS as an internal standard. FT-IR spectra were recorded between 4000 and 650 cm^{-1} on an FT-IR Nicolet 6700 apparatus with a Smart iTR accessory. Mass spectra were obtained on a Waters HPLC/MS system using the EI technique (70 eV). Thin layer chromatography was performed on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene/ethyl acetate solution (1:3 v/v) as the mobile phase.

2-(1-Hydroxy-1-phenylmethyl)-1,3,4-oxadiazoles **11a–d** were obtained from mandelic acid hydrazide and triethyl *ortho*esters according to a procedure described in the literature.[18]

4.2. Synthesis of α-bromophenylacetic acid 2

DL-Mandelic acid **1** (30.4 g; 0.20 mol) was gradually introduced into a solution of 40% HBr (56 mL) and concentrated H_2SO_4 (22 mL). The mixture was kept under reflux for 3 h, cooled and poured onto ice (150 g). The solution was then extracted twice with diethyl ether (2×75 mL), dried over $MgSO_4$ and concentrated on the rotary evaporator. The remaining brown solution was distilled under reduced pressure. The crude product was crystallised from hexane, yielding pure α-bromophenylacetic acid **2** as light-yellow crystals; yield: 75%, mp 83–84 °C (lit.:[34] mp 82–84 °C), R_f (benzene/ethyl acetate, 1:3 v/v) 0.70.

4.3. Synthesis of 1,1′-diphenylthiodiacetic acid 3

Freshly prepared NaSH, obtained by the saturation of methanolic $NaOCH_3$ with H_2S (3.53 g, 63 mmol), was dissolved in 50 mL of 20% NaOH and cooled. Then, α-bromophenylacetic acid **2** (26.9 g, 125 mmol) was slowly added and the reaction was stirred for 6 h. The resulting white suspension was refluxed for 1 h, cooled and treated with 50 mL of 30% H_2SO_4. The cold mixture was washed with diethyl ether (3×50 mL), dried over $MgSO_4$ and concentrated on the rotary evaporator. The crude product was crystallised from benzene, yielding pure 1,1′-diphenylthiodiacetic acid **3** as colourless crystals.

*4.3.1. 1,1′-Diphenylthiodiacetic acid (**3**).* Colourless needles, yield: 68%; mp 162–164 °C (lit.:[35] mp 164–165 °C); R_f (benzene/ethyl acetate, 1:3 v/v) 0.45; [Found: C, 63.49; H, 4.74. $C_{16}H_{14}O_4S$ requires C, 63.55; H, 4.67%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$

28.81 cm^{-1} M^{-1}), 223 (16.78); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.67 (1H, s, CH), 4.76 (1H, s, CH), 7.35–7.43 (10H, m, 2Ph), 11.50 (2H, br s, 2·OH); δ_C (DMSO-d_6) 57.2 (CH), 56.4 (CH), 128.3, 128.6, 128.7, 135.7 (2Ph), 171.0 (2·CO).

4.4. Synthesis of dimethyl 1,1′-diphenylthiodiacetate 4

1,1′-Diphenyl-2,2′-thiodiacetic acid **3** (24.2 g, 80 mmol), 120 mL of methanol and *p*-TsOH (0.50 g, 2.9 mmol) were heated under reflux for approximately 5 h. The methanol was then removed on the rotary evaporator. The residue was dissolved in 150 mL of diethyl ether, washed with a saturated aqueous Na_2CO_3 solution (50 mL) and then finally washed with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated on the rotary evaporator, yielding crude dimethyl 1,1′-diphenylthiodiacetate **4** as a yellow oil that crystallised upon resting. It was recrystallised from isopropanol.

*4.4.1. Dimethyl 1,1′-diphenylthiodiacetate (**4**).* Colourless solid, yield: 85%; mp 64–66 °C (lit.:[35] mp 69–71 °C); R_f (benzene/ethyl acetate, 1:3 v/v) 0.74; [Found: C, 65.48; H, 5.46. $C_{18}H_{18}O_4S$ requires C, 65.42; H, 5.50%]; λ_{max} (MeOH): 206.0 nm ($\varepsilon\times10^{-3}$ 31.43 cm^{-1} M^{-1}), 289 (0.43), 301 (0.25); δ_H (300 MHz, DMSO-d_6, Me_4Si) 3.64 (6H, s, 2OCH_3), 4.79 (2H, s, 2CH), 7.28–7.36 (10H, m, 2Ph); δ_C (DMSO-d_6) 52.4 (OCH_3), 73.1 (CH), 127.1, 127.4, 128.9, 128.9, 129.0, 130.0, 136.1, 136.1 (2Ph), 170.8, 171.1 (2·CO_{Ac}).

4.5. Synthesis of 1,1′-diphenylthiodiacetic acid dihydrazide 5

Dimethyl 1,1′-diphenylthiodiacetate **4** (21.5 g, 65 mmol) was dissolved in 150 mL of methanol. Then, 15 mL of hydrazine hydrate (310 mmol) was added, and the mixture was agitated at room temperature for 24 h. The white precipitate was removed by filtration, washed with diethyl ether and dried with air, yielding the crude dihydrazide with a melting point of 203–204 °C. The product was purified by crystallisation from methanol to give compound **5**.

*4.5.1. 1,1′-Diphenylthiodiacetic acid dihydrazide (**5**).* Colourless needles, yield: 76%; mp 209–210 °C, R_f (benzene/ethyl acetate, 1:3 v/v) 0.10; [Found: C, 58.25; H, 5.57; N, 16.88. $C_{16}H_{18}N_4O_2S$ requires C, 58.15; H, 5.50; N, 16.94%]; λ_{max} (MeOH): 212 nm ($\varepsilon\times10^{-3}$ 31.80 cm^{-1} M^{-1}); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.27 (2H, s, NH_2), 4.32 (1H, s, CH), 7.22–7.36 (5H, m, Ph), 9.37 (1H, s, NH); δ_C (DMSO-d_6) 51.9 (CH), 128.3, 128.8, 128.9, 138.2 (Ph), 168.9 (CO); *m*/*z* (EI) 63, 89, 121, 149, 181, 297, 298, 330 (M^+); ν_{max} (ATR) 3322, 3275, 1680, 1644, 1614, 1515, 1451, 1345, 1243, 1214, 1087, 995, 948, 921, 784, 739, 713, 697 cm^{-1}.

4.6. Reactions of 1,1′-diphenylthiodiacetic acid dihydrazide with triethyl *ortho*esters—general procedure

The starting 1,1′-diphenylthiodiacetic acid dihydrazide **5** (3.30 g, 10 mmol) was added to a mixture of the appropriate triethyl *ortho*ester (100 mmol) and 0.4 mL (0.40 g, 7 mmol) of glacial AcOH. The mixture was kept under reflux until the starting hydrazide was consumed (TLC, 5–15 h). After cooling and filtrating, the excessive *ortho*ester and AcOH were evaporated under reduced pressure. The crude products were purified by column chromatography with silica gel and an eluent of benzene/AcOEt (1:3). Pure products were crystallised from benzene/hexane mixtures.

*4.6.1. Bis(1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide (**6a**).* Colourless solid, yield: 80%; mp 198–200 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.50; [Found: C, 61.60; H, 4.00; N, 15.89. $C_{18}H_{14}N_4O_2S$ requires C, 61.69; H, 4.03; N, 15.98%]; λ_{max} (MeOH): 214 nm ($\varepsilon\times10^{-3}$ 30.92 cm^{-1} M^{-1}), 261 (1.61), 268 (1.26); δ_H (300 MHz, DMSO-d_6, Me_4Si) 5.83 (1H, s, CH), 7.32–7.42 (5H, m, Ph), 9.17 (1H, s, H–C5); δ_C (DMSO-d_6) 43.8 (CH–Ph), 128.0, 128.2, 129.0, 134.9 (Ph), 155.1 (C5), 164.5 (C2); *m*/*z* (EI) 56, 63, 89, 121, 159, 191, 317, 350 (M^+); ν_{max} (ATR) 3116, 2947, 1556, 1504, 1486, 1455, 1326, 1301, 1261, 1231, 1094, 1076, 1033, 974, 961, 874, 856, 832, 758, 723, 697 cm^{-1}.

*4.6.2. 2-Benzyl-1,3,4-oxadiazole (**7a**).* Colourless liquid, yield: 10%; R_f (benzene/ethyl acetate, 1:3 v/v) 0.66; [Found: C, 67.40; H, 5.00; N, 17.41. $C_9H_8N_2O$ requires C, 67.48; H, 5.04; N, 17.48%]; λ_{max} (MeOH): 208 nm ($\varepsilon\times10^{-3}$ 7.65 cm^{-1} M^{-1}); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.28 (2H, s, CH_2), 7.23–7.36 (5H, m, Ph), 9.13 (1H, s, H–C5); δ_C (DMSO-d_6) 31.1 (CH_2–Ph), 127.9, 129.4, 129.5, 135.2 (Ph), 155.4 (C5), 165.8 (C2); *m*/*z* (EI) 51, 63, 65, 77, 78, 89, 90, 91, 103, 104, 105, 118, 119, 131, 132, 159, 160 (M^+); ν_{max} (ATR) 3137, 3031, 1571, 1518, 1495, 1455, 1422, 1223, 1180, 1039, 980, 849, 878, 724, 695, 670 cm^{-1}.

*4.6.3. 2-Benzoyl-1,3,4-oxadiazole (**8a**).* Colourless solid, yield: 8%; mp 74–76 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.59; [Found: C, 61.99; H, 3.41; N, 16.02. $C_9H_6N_2O_2$ requires C, 62.05; H, 3.48; N, 16.08%]; λ_{max} (MeOH): 203 nm ($\varepsilon\times10^{-3}$ 10.36 cm^{-1} M^{-1}), 220 (6.47), 269 (10.50); δ_H (300 MHz, DMSO-d_6, Me_4Si) 7.63 (2H, t, *J* 7.8 Hz, H3′, H5′), 7.78 (1H, t, *J* 7.8 Hz, H4′), 8.36 (2H, d, *J* 7.8 Hz, H2′, H6′), 9.58 (1H, s, H–C5); δ_C (DMSO-d_6) 128.8, 130.5, 134.2, 134.8 (Ph), 155.7 (C5), 160.4 (C2), 177.7 (CO); *m*/*z* (EI) 51, 77, 90, 105, 146, 174 (M^+); ν_{max} (ATR) 3144, 1658, 1592, 1574, 1521, 1496, 1448, 1344, 1237, 1176, 1164, 1116, 1076, 1001, 978, 971, 911, 884, 810, 740, 684 cm^{-1}.

*4.6.4. Bis(5-methyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide (**6b**).* Colourless solid, yield: 70%; mp 120–123 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.34; [Found: C, 63.39; H, 4.70; N, 14.71. $C_{20}H_{18}N_4O_2S$ requires C, 63.45; H, 4.80; N, 14.80%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 37.44 cm^{-1} M^{-1}), 287 (0.55), 305 (0.47); δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.42 (3H, s, CH_3), 5.75 (1H, s, CH), 7.27–7.44 (5H, m, Ph); δ_C (DMSO-d_6) 11.1 (CH_3), 44.6 (CH–Ph), 128.8, 128.9, 129.6, 135.9 (Ph), 165.1 (C2), 165.4 (C5); *m*/*z* (EI) 56, 63, 89, 121, 135, 147, 160, 173, 205, 345, 378 (M^+); ν_{max} (ATR) 3226, 3030, 1670, 1587, 1558, 1495, 1454, 1368, 1261, 1225, 1076, 1031, 975, 954, 844, 737, 695, 681 cm^{-1}.

*4.6.5. 2-Benzyl-5-methyl-1,3,4-oxadiazole (**7b**).* Colourless liquid, yield: 18%, R_f (benzene/ethyl acetate, 1:3 v/v) 0.44; [Found: C, 68.88; H, 5.75; N, 16.01. $C_{10}H_{10}N_2O$ requires C, 68.94; H, 5.80; N, 16.07%]; λ_{max} (MeOH): 208 nm ($\varepsilon\times10^{-3}$ 11.1 cm^{-1} M^{-1}); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.45 (3H, s, CH_3), 4.14 (2H, s, CH_2), 7.29–7.31 (5H, m, Ph); δ_C ($CDCl_3$) 10.9 (CH_3), 31.7 (CH_2–Ph), 127.5, 128.7, 128.8, 133.9 (Ph), 164.1 (C5), 165.4 (C2); *m*/*z* (EI) 51, 63, 65, 77, 78, 83, 89, 90, 91, 103, 104, 105, 117, 118, 119, 131, 132, 145, 173, 174 (M^+); ν_{max} (ATR) 3031, 2919, 1594, 1567, 1496, 1455, 1426, 1391, 1351, 1224, 1167, 1076, 1048, 1029, 971, 959, 795, 728, 695, 667 cm^{-1}.

*4.6.6. 2-Benzoyl-5-methyl-1,3,4-oxadiazole (**8b**).* Colourless solid, yield: 10%; mp 103–105 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.68; [Found: C, 63.75; H, 4.23; N, 14.80. $C_{10}H_8N_2O_2$ requires C, 63.82; H, 4.30; N, 14.88%]; λ_{max} (MeOH): 203 nm ($\varepsilon\times10^{-3}$ 12.58 cm^{-1} M^{-1}), 270 (11.97); δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.65 (3H, s, CH_3), 7.60–7.80 (3H, m, H3′, H4′, H5′), 8.37 (2H, d, *J* 7.8 Hz, H2′, H6′); δ_C (DMSO-d_6) 11.4 (CH_3), 127.1, 129.5, 131.1, 135.4 (Ph), 161.8 (C2), 166.6 (C5), 178.3 (CO); *m*/*z* (EI) 51, 77, 90, 104, 105, 160, 188 (M^+); ν_{max} (ATR) 3218, 3069, 1666, 1596, 1575, 1558, 1524, 1451, 1394, 1364, 1306, 1261, 1229, 1171, 1092, 1049, 1003, 975, 913, 840, 804, 753, 738, 703, 687, 668 cm^{-1}.

*4.6.7. Bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide (**6c**).* Colourless solid, yield: 65%; mp 132–133 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.45; [Found: C, 64.92; H, 5.43; N, 13.79.

$C_{22}H_{22}N_4O_2S$ requires C, 65.00; H, 5.46; N, 13.77%]; λ_{max} (MeOH): 205 nm ($\varepsilon\times10^{-3}$ 30.63 cm^{-1} M^{-1}); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.32 (3H, t, *J* 7.5 Hz, CH_3), 2.79 (2H, q, *J* 7.5 Hz, CH_2), 5.39 (1H, s, CH), 7.33–7.44 (5H, m, Ph); δ_C ($CDCl_3$) 10.5 (CH_3), 19.0 (CH_2), 44.8 (CH–Ph), 128.5, 128.8, 129.0, 134.5 (Ph), 164.7 (C2), 168.7 (C5); *m*/*z* (EI) 56, 63, 89, 121, 187, 219, 247, 373, 406 (M^+); ν_{max} (ATR) 2992, 2946, 1577, 1548, 1493, 1453, 1378, 1298, 1177, 1074, 1024, 1000, 954, 864, 840, 798, 759, 731, 698, 672 cm^{-1}.

*4.6.8. 2-Benzyl-5-ethyl-1,3,4-oxadiazole (**7c**).* Colourless liquid, yield: 20%; R_f (benzene/ethyl acetate, 1:3 v/v) 0.56; [Found: C, 70.12; H, 6.40; N, 14.83. $C_{11}H_{12}N_2O$ requires C, 70.18; H, 6.44; N, 14.87%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 11.31 cm^{-1} M^{-1}); δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.18 (3H, t, *J* 7.5 Hz, CH_3), 2.73 (2H, q, *J* 7.5 Hz, CH_2), 4.21 (2H, s, CH_2), 7.20–7.38 (5H, m, Ph); δ_C (DMSO-d_6) 10.9 (CH_3), 18.9 (CH_2), 31.1 (CH_2–Ph), 127.7, 129.3, 129.4, 135.3 (Ph), 165.7 (C2), 168.4 (C5); *m*/*z* (EI) 51, 57, 65, 77, 89, 90, 91, 97, 103, 104, 105, 117, 118, 131, 132, 187, 188 (M^+); ν_{max} (ATR) 3011, 2983, 2942, 1589, 1564, 1496, 1455, 1426, 1381, 1192, 1165, 1075, 1029, 979, 962, 798, 727, 695 cm^{-1}.

*4.6.9. 2-Benzoyl-5-ethyl-1,3,4-oxadiazole (**8c**).* Colourless solid, yield: 10%; mp 63–65 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.59; [Found: C, 65.20; H, 4.85; N, 13.87. $C_{11}H_{10}N_2O_2$ requires C, 65.33; H, 4.99; N, 13.85%]; λ_{max} (MeOH): 203 nm ($\varepsilon\times10^{-3}$ 12.19 cm^{-1} M^{-1}), 218 (6.18), 269 (13.09); δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.33 (3H t, *J* 7.5 Hz, CH_3), 3.00 (2H, q, *J* 7.5 Hz, CH_2), 7.62 (2H, t, *J* 7.8 Hz, H3′, H5′), 7.77 (1H, t, *J* 7.8 Hz, H4′), 8.36 (2H, d, *J* 7.8 Hz, H2′, H6′); δ_C (DMSO-d_6) 10.2 (CH_3), 18.5 (CH_2), 128.8, 129.6, 130.4, 134.2, (Ph), 160.9 (C2), 169.4 (C5), 177.7 (CO); *m*/*z* (EI) 51, 77, 90, 97, 105, 117, 174, 202 (M^+); ν_{max} (ATR) 3064, 2994, 2162, 1664, 1595, 1575, 1551, 1521, 1450, 1429, 1397, 1385, 1326, 1279, 1169, 1076, 1034, 1011, 1001, 975, 913, 839, 806, 738, 689 cm^{-1}.

*4.6.10. Bis(5-phenyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide (**6d**).* Colourless solid, yield: 30%; mp 67–68 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.46; [Found: C, 70.92; H, 4.35; N, 10.93. $C_{30}H_{22}N_4O_2S$ requires C, 70.98; H, 4.37; N, 11.03%]; λ_{max} (MeOH): 204 nm ($\varepsilon\times10^{-3}$ 53.17 cm^{-1} M^{-1}), 252 (16.73), 297 (4.90), 309 (4.53); δ_H (300 MHz, $CDCl_3$, Me_4Si) 5.64 (1H, s, CH), 7.23–7.56 (8H, m, Ph, C5: H3′, H4′, H5′), 7.54–7.56 (3H, m, C5: H3′, H4′, H5′), 7.97 (2H, d, *J* 8.1 Hz, C5: H2′, H6′); δ_C ($CDCl_3$) 44.5 (CH–Ph), 126.9, 128.3, 128.4, 128.5, 128.7, 129.1, 135.1, 135.4 (2Ph), 165.3 (C2), 166.5 (C5); *m*/*z* (EI) 56, 63, 77, 89, 121, 235, 296, 343, 469, 502 (M^+); ν_{max} (ATR) 1572, 1553, 1495, 1454, 1329, 1266, 1175, 1076, 1028, 1009, 954, 868, 841, 732, 703, 698, 685, 668 cm^{-1}.

*4.6.11. 2-Benzyl-5-phenyl-1,3,4-oxadiazole (**7d**).* Colourless solid, yield: 49%; mp 109–110 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.54; [Found: C, 76.20; H, 5.10; N, 16.82. $C_{15}H_{12}N_2O$ requires C, 76.24; H, 5.13; N, 16.85%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 21.68 cm^{-1} M^{-1}), 251 (18.61); δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.34 (2H, s, CH_2), 7.34–7.36 (5H, m, Ph), 7.54–7.56 (3H, m, C5: H3′, H4′, H5′), 7.94 (2H, d, *J* 8.1 Hz, C5: H2′, H6′); δ_C (DMSO-d_6) 31.5 (CH_2–Ph), 124.0, 127.1, 127.9, 129.4, 129.6, 130.1, 132.6, 135.2 (2Ph), 164.9 (C5), 166.2 (C2); *m*/*z* (EI) 51, 63, 65, 77, 90, 91, 103, 145, 165, 178, 179, 209, 236 (M^+); ν_{max} (ATR) 1565, 1550, 1450, 1421, 1253, 1088, 1068, 1031, 798, 774, 729, 702, 692, 683, 661 cm^{-1}.

*4.6.12. 2-Benzoyl-5-phenyl-1,3,4-oxadiazole (**8d**).* Colourless solid, yield: 16%; mp 143–145 °C; R_f (benzene/ethyl acetate, 1:3 v/v) 0.61; [Found: C, 71.92; H, 3.95; N, 11.12. $C_{15}H_{10}N_2O_2$ requires C, 72.00; H, 4.03; N, 11.19%]; λ_{max} (MeOH): 207 nm ($\varepsilon\times10^{-3}$ 15.13 cm^{-1} M^{-1}), 235 (10.63), 290 (21.92); δ_H (300 MHz, DMSO-d_6, Me_4Si) 7.62–7.79 (6H, m, H3′, H4′, H5′, H3″, H4″, H5″), 8.12 (2H, d, *J* 6.6 Hz, C5: H2′, H6′), 8.40 (2H, d, *J* 6.9 Hz, C2: H2″, H6″); δ_C (DMSO-d_6) 122.6, 127.3, 128.8, 129.6, 130.5, 132.9, 134.3, 134.7 (2Ph), 160.8 (C2), 165.0 (C5), 177.6 (CO); *m*/*z* (EI) 51, 77, 103, 105, 145, 165, 222, 250 (M^+); ν_{max} (ATR) 3067, 2162, 1980, 1657, 1607, 1589, 1576, 1542, 1516, 1478, 1447, 1381, 1320, 1300, 1272, 1191, 1174, 1103, 1073, 1031, 1013, 1002, 988, 962, 929, 914, 857, 804, 776, 734, 708, 698, 678 cm^{-1}.

4.7. Synthesis and reactions of phenylacetic acid hydrazide 9 with triethyl *ortho*esters

The hydrazide of phenylacetic acid **9** was obtained according to the procedure described for hydrazide **4**. Commercially available ethyl phenylacetate reacted with hydrazine hydrate to yield white needles, yield: 86% yield, mp 120–121 °C (lit.:[46] mp 115–116 °C); R_f (benzene/ethyl acetate, 1:3 v/v) 0.10.

The starting phenylacetic acid hydrazide **9** (2.25 g, 15 mmol) was added to a mixture of the appropriate triethyl *ortho*ester (30 mmol), 5.0 mL of glacial AcOH and 30 mL of dry xylene. The reaction was kept under reflux until the starting hydrazide was consumed (TLC, 5–13 h). After cooling and filtrating, the excessive *ortho*ester and AcOH were evaporated under reduced pressure. The crude oily products (**7a**–**d**) were purified by column chromatography with silica gel and an eluent of benzene/AcOEt (1:3). The reactions gave the appropriate 5-substituted 2-benzyl-1,3,4-oxadiazoles: compound **7a** (colourless oil, 62% yield); **7b** (colourless oil, 77% yield); **7c** (colourless oil, 75% yield); **7d** (colourless needles, 85% yield, mp 108–110 °C).

4.8. Oxidation of 5-substituted 2-(1-hydroxy-1-phenylmethyl)-1,3,4-oxadiazole 11a–d with the use of $K_2Cr_2O_7/H_2SO_4$

To a solution of the appropriate 2-(1-hydroxy-1-phenylmethyl)-1,3,4-oxadiazole **11a**–**d** (12 mmol) in 15 mL of diethyl ether and 15 mL of benzene, the solution of $K_2Cr_2O_7$ (1.18 g, 4 mmol) in 6 mL of water and 1 mL of the concentrated H_2SO_4 was dropped in. The mixture was agitated at room temperature for 2 h. The organic layer was then separated, washed twice with water (2×30 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated on the rotary evaporator, yielding the crude products **8a**–**d**. They were crystallised from benzene/hexane mixtures, resulting in pure 2-benzoyl-1,3,4-oxadiazoles: compound **8a** (78% yield; mp 75–76 °C); **8b** (75% yield; mp 103–104 °C); **8c** (82% yield; mp 65–66 °C) and **8d** (88% yield; mp 144–145 °C).

4.9. The fission of 1,1′-diphenylthiodiacetic acid dihydrazide 5 in anisole or 2-phenoxyethanol

The starting 1,1′-diphenylthiodiacetic acid dihydrazide **5** (3.30 g, 10 mmol) was dissolved in 25 mL of the appropriate solvent (anisole, 2-phenoxyethanol), and the mixture was heated to reflux for 10 h. After cooling, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography with silica gel and an eluent of benzene/AcOEt (1:3). Phenylacetic acid hydrazide **9** (white needles, mp 119–120 °C) was obtained from anisole and 2-phenoxyethanol in 10% and 35% yields, respectively.

4.10. X-ray crystal structure analysis for 6c

The single crystals (0.25×0.19×0.17 mm) of bis(5-ethyl-1,3,4-oxadiazol-2-yl-phenylmethyl) sulfide **6c** were used for data collection at 293(2) K on a four-circle Oxford Diffraction Xcalibur diffractometer equipped with a two-dimensional area CCD detector with the graphite monochromatised Mo Kα radiation (λ=0.71073 Å) and the ω-scan technique. Integration of the intensities and correction for Lorenz and polarization effects were performed using the CrysAlis RED software.[47] Crystal structures were solved by direct methods and refined by a full-matrix least-

squares method on F^2 using the program SHELXL-97.[48] The H atoms were positioned geometrically and treated as riding on their parent C atoms with C–H distances of 0.93 Å (aromatic), 0.96 Å (CH_3), 0.97 Å (CH_2) and 0.98 Å (CH).

Empirical formula $C_{22}H_{22}N_4O_2S$, formula weight 406.51 g/mol, crystal system monoclinic, space group *C* 2/*c*, unit cell dimensions: a=22.3958(10), b=9.4855(2), c=10.9033(4) Å, β=118.556(6) °, V=2034.48(17) Å^3, Z=4, calculated density 1.327 Mg/m^3, absorption coefficient 0.185 mm^{-1}, F(000)=856, θ range for data collection: 3.51–25.00°, limiting indices: $-23\leq h\leq 26$, $-11\leq k\leq 11$, $-12\leq l\leq 12$, reflections collected/unique: 6161/1795 [R_{int}=0.0160], data/restraints/parameters: 1795/0/132, goodness-of-fit on F^2 1.122, final R indices [$I>2\sigma(I)$]: R_1=0.0397, wR_2=0.1050, R indices (all data): R_1=0.0439, wR_2=0.1071, largest diff. peak and hole: 0.277 and −0.244 e A^{-3}.

Complete crystallographic details are available as a Supplementary data, and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 819610) CCDC, 12 Union Road, Cambridge, CB21EZ, UK, e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Any request to the CCDC for this material should quote the full literature citation.

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