JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 1091–1098
Published online 28 June 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.829

The addition reaction of diamides to 1,2,5-thiadiazole 1,1-dioxide derivatives†

José A. Caram,[1] María V. Mirífico,[1,2] Silvia L. Aimone,[1] Oscar E. Piro,[3] Eduardo E. Castellano[4] and Enrique J. Vasini[1]*

[1]Instituto de investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Facultad de Ciencias Exactas, Departamento de Química, Universidad Nacional de La Plata, Casilla de Correo 16, Sucursal 4, (1900) La Plata, Argentina
[2]Facultad de Ingeniería, Departamento de Ingeniería Química, Universidad Nacional de La Plata, Calle 47 y 1, (1900) La Plata, Argentina
[3]Departamento de Física, Facultad de Ciencias Exactas, Universidad Nacional de La Plata and IFLP (CONICET), C. C. 67, (1900) La Plata, Argentina
[4]Instituto Física de São Carlos, Universidade de São Paulo, C.P. 369, 13560 São Carlos (SP), Brazil

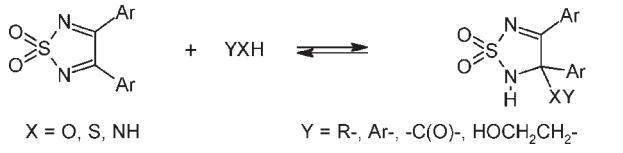
Received 10 February 2004; revised 10 April 2004; accepted 14 April 2004

ABSTRACT: The reactions of several derivatives of 1,2,5-thiadiazole 1,1-dioxide [3,4-diphenyl-(**1a**), 3,4-bis(*p*-methoxyphenyl)-(**1b**), phenanthro[9,10-*c*]-(**1c**) and acenaphtho[1,2-c]-1,2,5-thiadiazole 1,1-dioxide (**1d**), 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**2a**) and 4-ethoxy-5-methyl-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**2b**)], with reagents possessing two nucleophilic nitrogen atoms (urea, *N*,*N*′-dimethylurea, thiourea, *N*-methylthiourea, *N*-ethylthiourea, *N*-allylthiourea, *N*,*N*′-diethylthiourea, *N*,*N*′-diphenylthiourea, dithioxamide and sulfamide), were followed by cyclic voltammetry (CV) and UV–visible spectrophotometry in aprotic solvent solution. The products were isolated, characterized by IR, ^{1}H NMR and ^{13}C NMR methods and their structure was confirmed by single-crystal x-ray diffraction. Several substrate–nucleophile combinations (**1a–d** and **2a** with some ureas and thioureas) reacted to give good yields of new compounds formed by the addition reaction of the two nitrogen atoms of the nucleophile to the two >C═N— double bonds of the 1,2,5-thiadiazole 1,1-dioxide ring. Some systems (**1a**–dithioxamide and **2b**–thiourea) did not react, whereas in others (e.g. **1a**–sulfamide) a monoaddition equilibrium reaction was observed. Copyright © 2004 John Wiley & Sons, Ltd.
Additional material for this paper is available in Wiley Interscience

KEYWORDS: addition; diamides; 1,2,5-thiadiazole 1,1-dioxide derivatives

INTRODUCTION

Monofunctional alcohols, thiols, amines and amides add reversibly:



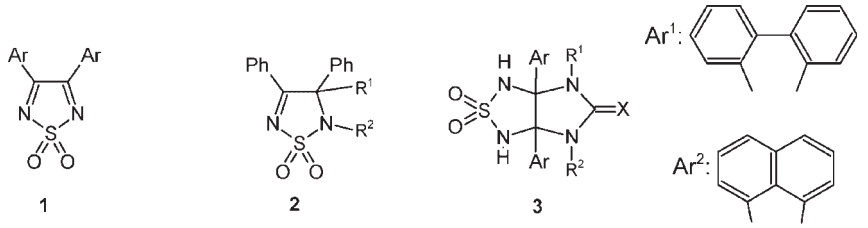
(1)

in aprotic solvent solution to only one of the two >C═N— double bonds of 1,2,5-thiadiazole 1,1-dioxide derivatives,[1–5] yielding carbon-substituted thiadiazolines. A difunctional nucleophile, ethylene glycol, in high relative concentration,[5] was also found to yield a monoaddition product. Consistently, the above-listed nucleophiles do not react, under similar conditions, with 1,2,5-thiadiazoline 1,1-dioxides (such as **2a** or **2b**, Scheme 1),[5] which have a single >C═N— double bond.

However, in Part I,[1] we reported that the reaction of **1a** (Scheme 1) with urea yielded 3a,6a-diphenyltetrahydroimidazo[4,5-*c*]-1,2,5-thiadiazol-5-one 2,2-dioxide (**3a**, Scheme 1), a bicyclic compound formed by the addition of urea, through both of its nitrogen atoms, to both heterocyclic double bonds of the substrate.

We report here the results of similar studies on the reactions of several derivatives of 1,2,5-thiadiazole 1,1-dioxide (see Scheme 1 for structures of reactants and products): 3,4-diphenyl-(**1a**), 3,4-bis(*p*-methoxyphenyl)-(**1b**), phenanthro[9,10-*c*]-(**1c**) and acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide (**1d**), 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**2a**) and 4-ethoxy-5-methyl-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**2b**), with

**Correspondence to:* E. J. Vasini, Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Facultad de Ciencias Exactas, Departamento de Química, Universidad Nacional de La Plata, Casilla de Correo 16, Sucursal 4, (1900) La Plata, Argentina.
E-mail: vasini@inifta.unlp.edu.ar
Contract/grant sponsors: Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET); Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CIC Pcia. Bs. As.); Universidad Nacional de La Plata (UNLP); FAPESP; CNPq.
†This is the second paper of a series. The first paper of the series[1] refers to the addition of amines and amides to 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide.



1

1a: Ar = Ar = Ph

1b: Ar = Ar = p-MeOPh

1c: Ar, Ar = Ar^1

1d: Ar, Ar = Ar^2

2

2a: $R^1 = R^2 = H$

2b: R^1 = Me; R^2 = OEt

3

3a: X=O; R^1=R^2=H; Ar = Ph

3b: X=S; R^1=R^2=H; Ar = Ph

3c: X=S; R^1=R^2=H; Ar = p-MeOPh

3d:X=S; R^1=Me; R^2=H; Ar = Ph

3e:X=S; R^1=Et; R^2=H; Ar = Ph

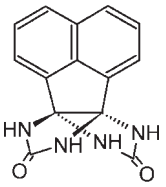
3f:X=S; R^1=Et; R^2=Et; Ar = Ph

3g:X=S; R^1=Allyl; R^2=H; Ar = Ph

3h:X=S; R^1=R^2=H; Ar,Ar = Ar^2

Scheme 1

reagents possessing two nucleophilic nitrogen atoms (urea, *N*,*N*′-dimethylurea, thiourea, *N*-methylthiourea, *N*-ethylthiourea, *N*-allylthiourea, *N*,*N*′-diethyltiourea, *N*,*N*′-diphenylthiourea, dithioxamide and sulfamide). The substrate–nucleophile systems **1a**, **1c** and **2a** with urea, **1a**–**d** and **2a** with thiourea and **1a** with *N*-methylthiourea, *N*-ethylthiourea, and *N*,*N*′-diethylthiourea formed bicyclic diaddition products in good yields. An equilibrium mono-addition reaction was observed between **1a** and sulfamide. The bisurea derivative **4** was the main product of the reaction of **1d** with urea (**4** has been synthesized by the reaction of acenaphthenequinone with urea in ethanol–water mixed solvent[6]), whereas no reaction took place for the **1a**–dithioxamide and the **1a**–*N*,*N*′-dimethylurea systems.



4

The nucleophilic addition reactions were followed using cyclic voltammetry (CV) and classical UV–visible spectrophotometric methods.

To the best of our knowledge, the synthetic reactions and compounds **3a**–**h** are new. A recent review[7] describes other bicyclic compounds, also containing urea and sulfamide moieties, obtained by the reaction of 4,5-dihydroxy-1,3-dialkylimidazolidin-2-one with *N*,*N*′-alkyl-substituted sulfamides,[8] and tri- and tetracyclic compounds obtained by the reaction of di- and tetra-*N*-hydroxymethyl-substituted bicyclic bisureas with sulfamide.[9] As is known, several 1,2,5-thiadiazolidine 1,1-dioxide derivatives are used as heart stimulants,[10] antiparasitics,[11,12] or β-lactamic antibiotics.[13] The 2-imidazolone ring is present in several biologically active molecules.[14–18] Moreover, an important number of thioureas with antitubercular, fungicide, herbicide and antiviral properties[19,20] have been reported. The combination of chemical functions in **3a**–**h** might endow these molecules with valuable biological effects.

RESULTS AND DISCUSSION

Urea, thiourea and monosubstituted and symmetrically disubstituted thioureas added to both >C═N— double bonds of 1,2,5-thiadiazole 1,1-dioxides to form bicyclic thiadiazolidines (**3**, Scheme 1) with good yield (ca 90%). The compounds were spectroscopically and analytically characterized, and the structure of seven of the eight synthesized compounds could be confirmed by single-crystal x-ray diffraction. In all cases, typical IR bands corresponding to NH, Ar, SO_2, and C═O or C═S were observed. ^{13}C NMR spectra showed sp^2 carbon atoms resonances (C═O or C═S) at ca 158 or 180 ppm, respectively, and the thiadiazolidine sp^3 carbon atoms were detected between 84 and 92 ppm.

Compound **3b** was also obtained by the reaction of thiourea with the thiadiazoline **2a**. This behavior was ascribed to the easy oxidation of **2a** (apparently by traces of dissolved oxygen) to **1a** in solution. In contrast, **2b**, which does not contain labile H atoms and is stable in solution, does not react with thiourea.

General structural characteristics of the compounds (x-ray diffraction results)

ORTEP[21] molecular drawings of **3a** and **h** [Fig. 1(a) and (b)] are used as example and reference for the structural

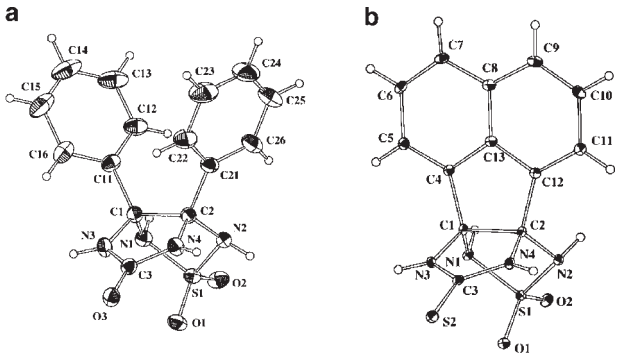


Figure 1. Molecular plots of (a) **3a** and (b) **3h** showing the labeling of the non-H atoms and their displacement ellipsoids at the 30% probability level

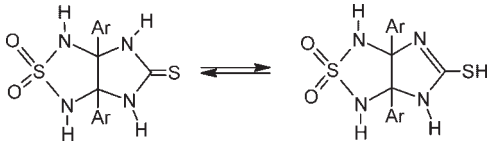
comments below. A CIF file for **3a–c**, **e–h** and corresponding XYZ files are available as electronic supplementary information (available in Wiley Interscience).

As expected, the urea or thiourea groups form planar five-membered rings with the heterocyclic (C1; C2) carbon atoms. These rings subtend dihedral angles in the 61–66° range with the N1C1C2N2 planes of the thiadiazolidine ring at the shared C1—C2 bond. The fused bicycle skeleton of all compounds (except **3f**) exhibit an approximate C_s symmetry, with the mirror plane bisecting the C1—C2 bond. All compounds crystallized in centrosymmetric space groups and therefore both stereoisomers of each molecule were present in the corresponding solid, even in the case of **3h**, where the asymmetry is probably present only in the solid state, as an effect of packing distortions. The thiadiazolidine cycle is bent around the N1···N2 'envelope' hinge in dihedral angles that range from ca 33 to 36°. The NH bonds present intermediate directions between near tetrahedral orientation around the nitrogen atom and the bisector of the S—N—C bond angle.

In the case of **3f**, because of the bulky ethyl groups, both heterocycle molecular fragments are appreciably twisted from a planar conformation in nearly equal torsion angles (−26.0° for the N1C1C2N2 thiadiazolidine group and −24.7° for the N3C1C2N4 thiourea group). Corresponding torsion angles for all the other compounds are less than 11°.

Bond lengths and angles in the thiadiazolidine fractions of the new compounds are similar to those found for the only two (to our knowledge) 1,2,5-thiadiazolidine 1,1-dioxides which were studied by x-ray diffraction.[22] Only the C1—C2 bond, which averages 1.62 Å, is appreciable longer than that previously measured (1.52 Å), but this is surely caused by the bulky 3,4-substituents in our compounds, that were not present in the reported thiadiazolidines.

A tautomeric equilibrium [Eqn (2)], similar to that known to exist in thiourea, is, in principle, possible in **3b–e**, **g**, **h**. However, no evidence of tautomerism was found by x-ray diffraction. Also, no evidence was found for the asymmetric isomers which might form through the attack of the HN═C(SH)—NH_2 thiourea tautomer.


(2)

Voltammetric measurements

Typical changes in the CV response caused by the addition of nucleophiles to the >C═N— bonds of the thiadiazole 1,1-dioxide ring were observed in our studies of the voltammetric behavior of **1a**. Briefly, these changes are as follows: **1a** in aprotic solvent solution presents two reversibly couples, their corresponding cathodic peaks (Ic and IIc, at ca −0.9 and −1.4 V vs Ag^+/Ag) were assigned to the formation, respectively, of the radical anion and the dianion of the substrate. On addition to one of the >C═N— double bonds, a thiadiazoline is formed. Thiadiazolines present two cathodic peaks (IIIc and IVc) at about −1.7 to −2.2 V. Peaks Ic, IIIc and IVc are typically observed in solutions of a thiadiazole and a monofunctional nucleophile (i.e. in thiadiazole–thiadiazoline mixtures). These peaks can be employed [see Eqn (6) below] to estimate equilibrium constants for monoaddition reactions[1–5] [Eqn (1)]. We have verified that under similar experimental conditions, the corresponding totally saturated compounds, 1,2,5-thiadiazolidine 1,1-dioxides, either do not present voltammetric signals or show an ill-defined cathodic peak at potentials ca −2.4 V or lower, that frequently appears as a shoulder on the background current of the solvent.

Experimental voltammograms of a solution of **1a** and thiourea (molar ratio [thiourea]/[**1a**] = 10) in DMF at several reaction times are presented in Fig. 2. A gradual

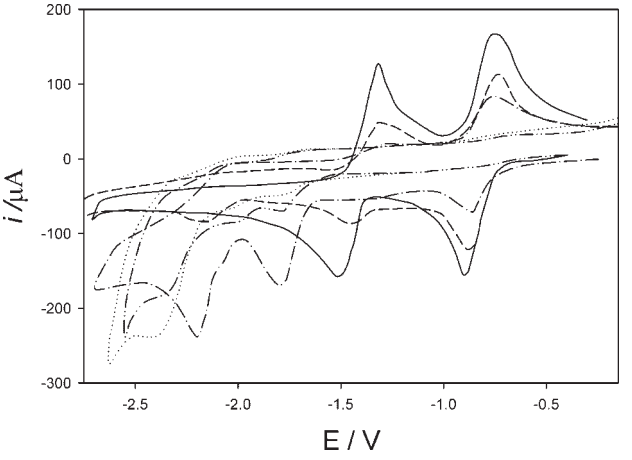
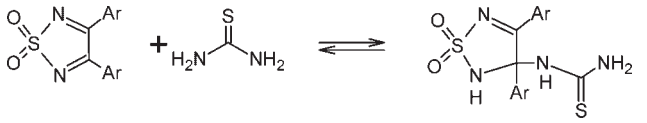


Figure 2. Time evolution of the cyclic voltammogram of an 11.9 mM solution of **1a** in DMF on thiourea addition ([thiourea] = 0.12 M). (—) Before addition; (- - -), 1 h; (- · -), 5.5 h; (- · · -), 20 days; (· · · ·), 90 days after addition. Sweep rate, 0.2 V s^{-1}

disappearance of the **1a** peaks (solid line, initial CV) was observed, along with the appearance of two thiadiazoline cathodic peaks at −1.7 and −2.1 V (i.e. dashed-dotted line, at 5.5 h). As noted above, the voltammogram at 5.5 h, presenting peaks Ic, IIIc and IVc, is typical of a thiadiazole–thiadiazoline mixture. The intensity of these peaks decreased thereafter, while a peak at −2.4 V appeared (dashed-two dotted and dotted lines, 20 and 90 days).

The time evolution of the CV of **1a** solutions in DMF, on the addition of urea or substituted thioureas, or of **1d** solutions, on addition of thiourea was similar to that shown in Fig. 2 for the **1a**–thiourea system. These experiments suggested a stepwise mechanism, with an intramolecular second step, as outlined in Eqns (3) and (4) for **1a** and thiourea.



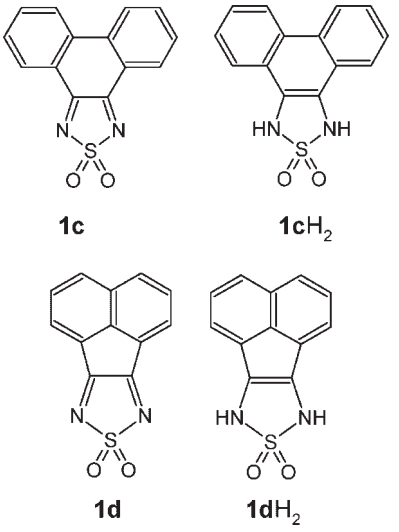
(3)

(4)

The spectrophotometric results for the **1a**–urea system presented below are also in agreement with this mechanism.

The reactions are reversible in solution and the equilibrium is shifted to the reactants by a temperature increase: a 3.54 mM solution of **3b** in DMF, with 0.1 M $NaClO_4$ as supporting electrolyte, presented a featureless CV between 0.9 and −2.8 V but, after heating the solution at 105°C for 3 h, the CV registered immediately after the solution had been rapidly cooled to room temperature showed the Ic and IIc cathodic voltammetric peaks of **1a** and the anodic peak of thiourea at ca 0.3 V. Likewise, a DMF solution of **1a** (42 mM) and urea (0.3 M), with 0.2 M $NaClO_4$ as supporting electrolyte, was left to react until an almost flat CV was observed, after the solution had been heated to 90°C for 3 h. When rapidly cooled and scanned, the CV showed the typical voltammogram of a mixture of **1a** and its corresponding (monoaddition) thiadiazoline, i.e. peaks Ic, IIIc and IVc.

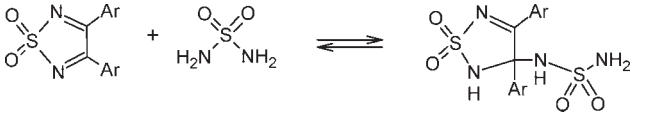
As mentioned, **1d** reacted with thiourea to give **3h** (Scheme 1). However, **1c**, which also has a 3,4-substituent with a fused π-system, reacted differently: attempts to isolate the corresponding bicycle by the standard method (see Experimental) gave a reduction product of **1c**, the thiadiazoline **1c**H_2 (Scheme 2), which we have recently synthesized and identified.[23] It should be noted, as we have reported, that thiadiazoline **1c**H_2 differs from the typical 1,2,5-thiadiazoline structure, since both



Scheme 2

carbon–nitrogen bonds are single, and a sulfur precipitate was also observed. The difference is presumably caused by the resonance stability provided by the phenanthrene group in **1c**H_2, whereas in a hypothetical **1d**H_2 (Scheme 2), the resulting acenaphtylene group would not represent an appreciable aromaticity increase over the original naphthalene group.

The voltammetric response of the **1a**–sulfamide system suggested that only monoaddition [Eqn (5)] took place.



(5)

In effect, the changes in the CV of solutions of **1a** on addition of sulfamide (shown in Fig. 3) were similar to those found when alcohols were added to solutions of **1a** as described in the first paragraph of this section (i.e.

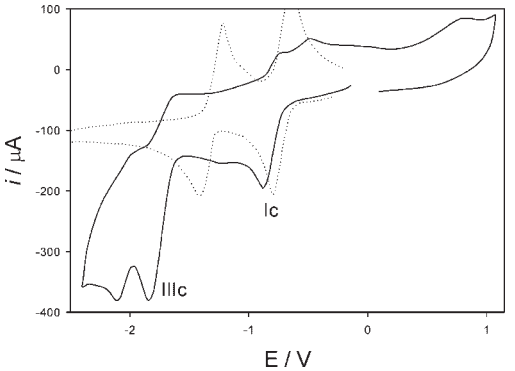


Figure 3. Equilibrium cyclic voltammogram of a **1a** (9.32 mM)-sulfamide (1.13 M) solution in DMF (solid line). Sweep rate, 0.2 V s^{-1}; supporting electrolyte, 0.14 M $NaClO_4$. A cyclic voltammogram of **1a** (dotted line) under similar experimental conditions is shown for comparison

formation of a thiadiazoline 1,1-dioxide from a thiadiazole 1,1-dioxide). As reported for these reactions,[24] the equilibrium constant can be estimated from cyclic voltammetric data using Eqn (6) [ν = sweep potential rate; i(Ic), i(IIIc) = current intensity of labeled voltammetric peaks in Fig. 3].

$$K[\text{sulfamide}]_0 = \frac{2\{i(\text{IIIc})/v^{1/2} + i(\text{Ic})/2v^{1/2}\}}{i(\text{Ic})/v^{1/2}} \qquad (6)$$

The linear dependence of the current intensity of peaks Ic and IIIc with $v^{1/2}$ [a requisite for the employment of Eqn (6)] was verified in the experimental sweep rate range (0.05–0.3 V s^{-1}). The calculated equilibrium constant K(**1a**–sulfamide), was 3.8 ± 0.4 M^{-1}. This value is similar to that obtained with other N- or O-nucleophiles.[1,2]

Solutions of **1a** and dithioxamide presented cyclic voltammograms that remained unchanged for several months, indicating lack of reaction. A similar behavior was observed for the **1a**–*N*,*N*′-dimethylurea system. However, probably owing to the greater nucleophilicity of the N atoms of thioureas, as compared with those of ureas, *N*,*N*′-diethylthiourea yielded **3f**. Also, the cyclic voltammograms of the **1a**–*N*,*N*′-diphenylthiourea system evolved similarly to the **1a**–thiourea system, suggesting the formation of the corresponding bicyclic compound, which, however, was apparently unstable and could not be isolated.

Spectrophotometric results

Compound **1a** in aprotic solvent solution presents a UV band at ca 325 nm, with a molar absortivity (ε) of ca 9000 M^{-1} cm^{-1}, thiadiazoline **1a**H_2 has an intense absorption band at ca 260 nm, with $\varepsilon \approx 15\,000$ M^{-1} cm^{-1}, while saturated thiadiazolidine 1,1-dioxides absorb very weakly in the same spectral region [ε(260 nm) ≈ 500 M^{-1} cm^{-1}). Thus, the reaction of **1a** with urea in MeCN–DMF (1:2) mixed solvent solution could be followed by UV spectrophotometry. The MeCN–DMF (1:2) mixed solvent used was a convenient experimental compromise: DMF alone would have masked the spectrum because of its UV absorption (the mixed solvent cutoff was ca 255 nm). However, even though MeCN, which does not absorb in the region of interest, the reaction was found to be very slow in this solvent (times of the order of months, versus days in DMF). The results are shown in Fig. 4: a band at 325 nm (corresponding to **1a**), which was initially observed, decreased as the reaction advanced. Simultaneously, a band at 260 nm appeared and increased. The first three spectra (covering a lapse of 14 days) coincide at an isosbestic point (ca 272 nm). This is the typical spectral behavior of monoaddition reactions to **1a**,[2] indicating the slow conversion of **1a** to the **1a**–urea monoaddition compound. At prolonged reaction times, the bicyclic thiadiazolidine **3a** was formed and the band at 260 nm decreased greatly in intensity.

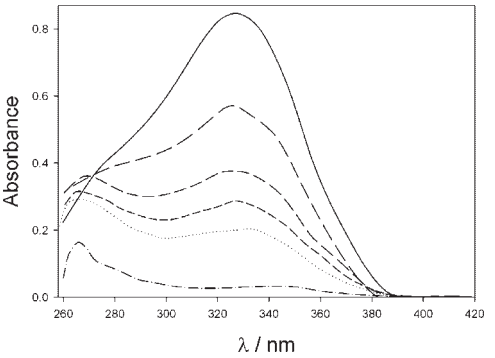


Figure 4. UV spectrum of a solution of **1a** (0.10 mM and urea (7.1 mM) in mixed DMF–MeCN (1:2) solvent. Solid line, initial spectrum; long dashed line 6; medium dashed line 14; short dashed line 20; dotted line, 27; dashed-dotted line, 41 days after solution preparation

CONCLUSIONS

Bicyclic compounds that are structurally related to biologically active molecules were obtained in very good yields by simple reactions of 1,2,5-thiadiazole 1,1-dioxides with urea and thioureas. The reactions involved the nucleophilic attack of both N atoms of the nucleophile on both >C═N— double bonds of the substrate. Probably because of the greater nucleophilicity of the N atoms of thioureas than those of ureas, the reaction was about 10 times faster with thioureas and, under similar conditions, a sterically hindered thiourea (1,2-diethylthiourea) reacted, but a similarly hindered urea (*N*,*N*′-dimethylurea) did not.

Theoretical calculations in progress in our group are aimed at comparing relative stabilities of monoaddition compounds, diaddition compounds of monofunctional nucleophiles and cyclic compounds of difuntional nucleophiles.

EXPERIMENTAL

Compounds **1a–d** and **2a**, **b** were synthesized, purified and characterized according to standard methods.[25] Standard methods[26–28] were used for the purification of commercial solvents, ureas and thioureas. The solvents were dried with activated 4A molecular sieves and stored under a dry nitrogen atmosphere. Their water content was <50 ppm (Karl Fischer).

A Cary 3 UV–visible spectrophotometer equipped with thermostated cell holders and PTFE-stoppered quartz cells of 1 cm optical pathlength was used.

^{1}H and ^{13}C NMR spectra were measured with a Bruker 200 MHz instrument and IR spectra with a Shimadzu IR-435 spectrophotometer.

CV experiments were performed in a conventional undivided gas-tight glass cell with dry nitrogen gas inlet and outlet. The working electrode was a 3 mm diameter vitreous carbon disk encapsulated in PTFE, the counter-electrode was a 2 cm^2 Pt foil and an Ag^+ (0.1 M, MeCN)/Ag reference electrode (to which all potentials reported are referred) was used. The supporting electrolyte was 0.1 M $NaClO_4$. An LYP-M2 potentiostat, a three-module LYP sweep generator and a Houston Omnigraphic 2000 pen recorder were used. The preparation of solutions, the CV experiments and other manipulations were carried out in a glove-box under a dry nitrogen atmosphere.

Single crystals for x-ray diffraction studies (of seven out of the eight synthesized compounds) could be obtained from ethanol or MeCN solutions by slow evaporation of the solvent. Details of the crystal structure determination are given below. General structural characteristics of the compounds were commented on above (see Results and discussion).

Synthesis of compounds

Compounds **3a**–**h** were obtained in high yield by a general procedure, exemplified here for **3b**: **1a** (0.150 g; 0.56 mmol) and thiourea (0.211 g; 2.77 mmol) were mixed with 1–2 ml of DMSO or DMF at room temperature. The initial suspension turned into a homogeneous solution in a day. On addition of water (ca 5 ml), a precipitate was obtained. The precipitate was filtered and washed thoroughly with water. A 0.179 g amount (93% yield) of solid (TLC pure) **3b** was obtained. Compound **4** was obtained by the same procedure through the mixture of similar molar proportions of **1d** and urea in 2 ml of DMSO.

Compound **3b** could also be obtained by the reaction of **2a** with thiourea in DMSO solution, by a similar procedure (yield: 90%).

3a: m.p. 310–312°C (decomp.); ν_{max} (KBr) (cm^{-1}), 3355 and 3325 (s, NH), 3050 (br, $C_{Ar}H$); 1700 (s, C═O), 1495 and 1440 (vw; s, arom. ring str.), 1410 (m), 1395, 1380 and 1360 (m, thiadiazolidine ring), 1320 and 1180 (s, SO_2); δ_H (200 MHz; DMSO-d_6, Me_4Si), 7.06–7.76 (10 H, m, Ph), 8.50 and 7.97 (2H + 2H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 159.6 (C═O), 127.2–137.5 (Ph), 83.8 (Ph–*C*–*C*-Ph). Found: C, 54.60; H, 4.17; N, 18.18; S, 10.01. Calc. for $C_{15}H_{14}N_4O_3S$: C, 54.54; H, 4.24; N, 16.97; S, 9.70%.

3b (yield 93%): m.p. 243–245°C (decomp.); ν_{max}(KBr) (cm^{-1}), 3600 and 3300 (m; s, NH), 1610, 1510 and 1440 (m; s; s, arom. ring str.), 1365 (s, thiadiazolidine ring), 1290 and 1150 (s, SO_2), 1200 (m), 1035 (s, C═S); δ_H (200 MHz; DMSO-d_6, Me_4Si), 7.06–7.10 (10 H, m, Ph), 8.80 and 9.68 (2H + 2H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 182.3 (C═S), 127.0–136.2 (Ph), 86.9 (Ph–*C*–*C*–Ph). Found: C, 49.44; H, 4.51; N, 15.51; S, 18.50. Calc. for $C_{15}H_{14}N_4O_2S_2{\cdot}H_2O$: C, 49.43; H, 4.43; N, 15.37; S, 17.60%.

3c (yield 93%): m.p. 174–175°C (decomp.); ν_{max}(KBr) (cm^{-1}), 3400 and 3275 (m; s, NH), 2950 and 2800 (vw, CH), 1610, 1585, 1515 and 1445 (s; m; vs; m, arom. ring str.), 1420 (m), 1395 and 1365 (m, thiadiazolidine ring), 1310 and 1175 (s, SO_2), 1295 (s), 1270 (s), 1210 (m), 1050 (m, CN), 1040 (m, C═S); δ_H (200 MHz; DMSO-d_6, Me_4Si), 3.63 (6 H, s, CH_3O), 6.65–6.98 (8 H, m, Ph), 8.65 and 9.56 (2H + 2H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 182.1 (C═S), 159.1–112.7 (Ph), 86.7 (Ph–*C*–*C*–Ph), 55.0 (CH_3O). Found: C, 50.35; H, 4.86; N, 14.61; S, 17.92. Calc. for $C_{17}H_{18}N_4O_4S_2$: C, 50.24; H, 4.43; N, 13.79; S, 15.76%.

3d (yield 91%): m.p. 220–221°C (decomp.); ν_{max}(KBr) (cm^{-1}), 3250 and 3100 (s, NH), 3030 (s, $C_{Ar}H$), 2655 and 1480 (w, s, $C_{Aliph}H$), 1495 and 1455 (s, arom. ring str.), 1410 (m), 1385 (s, thiadiazolidine ring), 1310 and 1170 (s, SO_2), 1230 (m), 1055 (s, CN), 1035 (m, C═S); δ_H (200 MHz; DMSO-d_6, Me_4Si), 2.89 (3H, s, CH_3), 6.83–7.16 (10H, m, Phs), 8.92, 9.25 and 9.81 (1H + 1H + 1H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 182.0 ppm (C═S), 126.6–136.0 (Ph), 89.6 and 84.6 (bridgehead C atoms), 29.3 (CH_3). Found: C, 52.42; H, 4.44; N,15.89; S, 18.11. Calc. for $C_{16}H_{16}N_4O_2S_2$: C, 53.33; H, 4.44 N, 15.56; S, 17.78%.

3e (yield 94%): m.p. 202–205°C (decomp.); ν_{max} (KBr) (cm^{-1}), 3300 (s, NH), 3050 (s, $C_{Ar}H$), 1470 (s, $C_{Aliph}H$), 1500 and 1450 (s, arom. ring str.), 1430 (m), 1380 (s, thiadiazolidine ring), 1330 (m), 1310 and 1150 (s, SO_2), 1270 (w), 1210 (m), 1060 (s, C—N), 1035 (vw, C═S); δ_H (200 MHz; DMSO-d_6, Me_4Si), 1.17–1.22 (3H, t, CH_3), 2.98–3.12 and 3.65–3.79 (2H, m, CH_2), 6.85–7.19 (10H, m, Phs), 8.91, 9.25 and 9.72 (1H + 1H + 1H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 181.7 ppm (C═S), 126.8–136.2 (Ph), 90.3 and 84.4 (bridgehead C atoms) and 13.2 (*C*H_3–CH_2–), the CH_2 resonance is hidden by the DMSO solvent signals. Found: C, 53.12; H, 4.82; N, 15.07; S, 16.44. Calc. for $C_{17}H_{18}N_4O_2S_2$: C, 54.54; H, 4.81; N, 14.97; S, 17.11%.

3f (yield 95%): m.p. 194–196°C (decomp.); ν_{max} (KBr) (cm^{-1}) 3300 and 3125 (s, NH), 3000 (m, $C_{Ar}H$), 2950, 2750 and 1460 (m; w; s, $C_{Aliph}H$), 1415 (m), 1475 and 1445 (arom. ring str.), 1395, 1380 and 1365 (s, thiadiazoline ring), 1345 (s), 1310 and 1175 (s, SO_2), 1265 (s), 1215 (m), 1045 (m, C═S); δ_H (200 MHz; DMSO-d_6, Me_4Si), 1.21–1.26 (6H, t, CH_3), 3.11–3.25 and 3.57–3.71 (4H, m, CH_2), 6.91–7.13 (10H, m, Phs), 9.24 (2H, s, NH); δ_C (200 MHz; DMSO-d_6, Me_4Si), 182.6 (C═S), 127.5–134.2 (Ph), 88.7 (bridgehead C atoms), and 13.3 (*C*H_3–CH_2–), the CH_2 resonance is hidden by the DMSO solvent signals. Found: C, 56.18; H, 5.48; N, 14.12; S, 15.43. Calc. for $C_{19}H_{22}N_4O_2S_2$: C, 56.69; H, 5.51; N, 13.92; S, 15.93%.

3g (yield 81.3%): m.p. 190–194°C (decomp.); ν_{max}(KBr) (cm^{-1}) 3300 (s, NH), 3050 (w, $C_{Ar}H$), 2850, 2650 and 1460 (s; m; s, $C_{Aliph}H$), 1500 and 1450 (s, arom. ring str.), 1410 (m), 1380 (s, thiadiazolidine ring), 1340 (m), 1320 and 1160 (s, SO_2), 1250 (w), 1210 (s); δ_H (200 MHz; DMF-d_7, Me_4Si), 3.91–3.99 and 4.41–4.50 (4H, m, CH_2), 4.96–5.23 (2H, m, CH_2═), 5.83–6.12 (1H, m, ═CH–), 7.03–7.81(10H, m, Ph), 9.06 and 9.77 (2H + 1H, s, NH); δ_C (200 MHz; DMF-d_7, Me_4Si), 183.6 (C═S), 137.3 (═CH–), 134.8–127.9 (Ph), 117.1 (CH_2 =), 91.7 and 85.8 (bridgehead C atoms) and 47.4 (–CH_2–). Found: C, 55.39; H, 4.97; N, 14.53; S, 16.59. Calc. for $C_{18}H_{18}N_4O_2S_2$ C, 55.94; H, 4.69; N, 14.50; S, 16.59%.

3h (yield 88%): m.p. 249–250°C (decomp.); ν_{max} (KBr) (cm^{-1}), 3400, 3380 and 3200 (s, NH), 3050 (m, $C_{Ar}H$), 1480 (s, arom. ring str.), 1410 (s), 1395 (s), 1320 and 1180 (s, SO_2), 1120 (s), 1070 (s); δ_H (200 MHz; DMSO-d_6, Me_4Si), 9.84 and 8.70 (2H + 2H, s, NH) and 7.52–7.96 (6H, m, Ph); δ_C (200 MHz; DMSO-d_6, Me_4Si), 180.8 (C═S), 152.6, 139.0–120.5 (arom. ring) and 90.43 (Ph–*C*–*C*–Ph). Found: C, 46.71; H, 3.42; N, 16.98; S, 26.87. Calc. for $C_{13}H_{10}N_4O_2S_2$: C, 49.04; H, 3.17; N, 17.60; S, 20.14%.

4 (yield 49%): ν_{max} (KBr) (cm^{-1}), 3250 and 3100 (s, NH), 1660 (s, C═O), 1500 and 1450 (m, arom. ring str.), 1415 (m), 1380 (m), 1360 (m), 1340 (m), 1260 (m), 1190 (s), 1100 (s); δ_H (200 MHz; DMSO-d_6, Me_4Si): 6.28 (2H, s, NH) and 7.45–7.81 (6H, m, Phs); δ_C (200 MHz; DMSO-d_6, Me_4Si), 157.7 (C═O), 143.3–118.8 (6 signals, acenaphthyl) and 92.23 (bridgehead C atoms).

Crystal structure determination of compounds 3a, b and d–h

The x-ray diffraction patterns of **3b** and **3g** were measured with an Enraf-Nonius CAD4 x-ray diffractometer, employing the $\omega - 2\theta$ scan mode and Cu Kα, graphite monochromatized, radiation ($\lambda = 1.54184$ Å). The rest of the compounds were measured with a Enraf-Nonius KappaCCD diffractometer, working in the φ and ω scan modes with Mo Kα, graphite monochromatized radiation ($\lambda = 0.71073$ Å). CAD4 and KappaCCD data were reduced with the XCAD4[29] and DENZO & SCALEPACK[30] programs, respectively. The structures were solved by direct methods employing SHELXS[31] and refined by full-matrix least-squares with the SHELXL[32] program.

All but the thiadiazoline and water hydrogen atoms were included in the molecular models at stereochemical positions and refined with the riding model. The thiadiazoline hydrogen atoms of all compounds along with one water H atom of **3b** were found in a difference Fourier map and refined isotropically with N—H and Ow—H distances constrained to target values of 0.89(1) and 0.82(1) Å, respectively.

Crystal data

3a: $C_{15}H_{14}N_4O_3S$, $M = 330.36$, monoclinic, $a = 9.948(1)$, $b = 13.039(1)$, $c = 12.675(1)$ Å, $\beta = 109.63(1)°$, $U = 1548.6(1)$ Å^3, $T = 293(2)$ K, space group $P2_1/c$ (No. 14), $Z = 4$, μ(Mo Kα) = 0.230 mm^{-1}, 14 437 reflections measured, 3548 unique ($R_{int} = 0.039$) which were used in all calculations. The final $wR(F^2)$ was 0.112 (all data).

3b: $C_{15}H_{14}N_4O_2S_2{\cdot}H_2O$, $M = 364.44$, orthorhombic, $a = 17.096(1)$, $b = 10.800(3)$, $c = 17.868(2)$ Å, $U = 3298.8(9)$ Å^3, $T = 293(2)$ K, space group *Pbca* (No. 61), $Z = 8$, μ(Cu Kα) = 3.129 mm^{-1}, 3141 reflections measured, 2972 unique ($R_{int} = 0.035$). Final $wR(F^2) = 0.1297$.

3d: $C_{16}H_{16}N_4O_2S_2$, $M = 360.45$, monoclinic, $a = 10.537(1)$, $b = 14.709(1)$, $c = 11.425(1)$ Å, $\beta = 111.153(1)°$, $U = 1651.4(1)$ Å^3, $T = 100(2)$ K, space group $P2_1/n$ (No. 14), $Z = 4$, μ(Mo Kα) = 0.339 mm^{-1}, 15 578 reflections measured, 3229 unique ($R_{int} = 0.048$). Final $wR(F^2) = 0.0855$.

3e: $C_{17}H_{18}N_4O_2S_2$, $M = 374.47$, monoclinic, $a = 10.5263(2)$, $b = 15.3045(4)$, $c = 11.6783(3)$ Å, $\beta = 112.071(1)°$, $U = 1743.50(7)$ Å^3, $T = 100(2)$ K, space group $P2_1/n$ (No. 14), $Z = 4$, μ(Mo Kα) = 0.324 mm^{-1}, 10 795 reflections measured, 3396 unique ($R_{int} = 0.047$). Final $wR(F^2) = 0.0932$.

3f: $C_{19}H_{22}N_4O_2S_2$, $M = 402.53$, monoclinic, $a = 12.759(1)$, $b = 9.530(1)$, $c = 16.027(1)$ Å, $\beta = 103.96(1)°$, $U = 1891.2(2)$ Å^3, $T = 100(2)$ K, space group $P2_1/c$ (No. 14), $Z = 4$, μ(Mo Kα) = 0.304 mm^{-1}, 9262 reflections measured, 3288 unique ($R_{int} = 0.070$). Final $wR(F^2) = 0.1183$.

3g: $C_{18}H_{18}N_4O_2S_2$, $M = 386.48$, monoclinic, $a = 10.523(1)$, $b = 8.333(1)$, $c = 20.681(3)$ Å, $\beta = 90.27(1)°$, $U = 1813.5(4)$ Å^3, $T = 293(2)$ K, space group $P2_1/c$ (No. 14), $Z = 4$, μ(Mo Kα) = 2.839 mm^{-1}, 3250 reflections measured, 3074 unique ($R_{int} = 0.008$). Final $wR(F^2) = 0.1065$.

3h: $C_{13}H_{10}N_4O_2S_2$, $M = 318.37$, orthorhombic, $a = 10.3017(1)$, $b = 18.7506(1)$, $c = 13.2639(1)$ Å, $U = 2562.10(3)$ Å^3, $T = 100(2)$ K, space group *Pbca* (No. 61), $Z = 8$, μ(Mo Kα) = 0.426 mm^{-1}, 39 084 reflections measured, 2253 unique ($R_{int} = 0.052$). Final $wR(F^2) = 0.1060$.

Acknowledgments

This work was financially supported by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CIC Pcia. Bs. As.), the Universidad Nacional de La Plata (UNLP), Facultad de Ciencias Exactas, Departamento de Química and Facultad de Ingeniería, Departamento de Ingeniería Química, FAPESP of Brazil and the collaborative agreement between CONICET of Argentina and CNPq of Brazil. M.V.M, J.A.C. and O.E.P. are researchers of CONICET

and UNLP and E.J.V. is a researcher of CIC Pcia. Bs. As. and UNLP.

The authors acknowledge the late Professor Dr E. G. Gros (UMyMFOR, Universidad de Buenos Aires, CONICET) and LASEICIC (CIC Pcia. Bs. As.) for magnetic resonance spectroscopic measurements and Professor Alzir Acevedo Batista, Departamento de Química, Universidad Federal de São Carlos, São Carlos, Brazil, for elemental analyses.

REFERENCES

1. Caram JA, Aimone SL, Mirífico MV, Vasini EJ. *J. Phys. Org. Chem.* 2003; **16**: 220–225.
2. Mirífico MV, Vasini EJ, Sicre JE. *J. Phys. Org. Chem.* 1993; **6**: 341–346.
3. Mirífico MV, Caram JA, Vasini EJ. *Atual Fis.-Quim. Org.* 1993; 184–200.
4. Caram JA, Mirífico MV, Aimone SL, Vasini EJ. *Can. J. Chem.* 1996; **74**: 1564–1571.
5. Aimone SL, Caram JA, Mirífico MV, Vasini EJ. *J. Phys. Org. Chem.* 2000; **13**: 272–282.
6. Gompper R, Nöth H, Rattay W, Schwarzensteiner ML, Spes P, Wagner HU. *Angew. Chem., Int. Ed. Engl.* 1987; **26**: 1039–1041.
7. Gazieva GA, Kravchenko AN, Lebedev OV. *Russ. Chem. Rev.* 2000; **69**: 221–230.
8. Orekhova GA, Kravchenko AN, Lebedev OV. In *IXth Conference of Organic Chemistry and Biochemistry for Young Scientists (Abstracts of Reports)*, Liblice, 1995; 111.
9. Gazieva GA, Kravchenko AN, Chegnev KY, Strelenko YA, Lebedev OV. *Mendeleev Commun.* 2000; **10**: 28–29.
10. Lumma WC Jr, Anderson PS, Baldwin JJ, Bolhofer WA, Habecker CH, Hirsfield JM, Pietruszkiewicz AM, Randall WC, Torchiana ML, Britcher SF, Clineschmidt BV, Denny GH, Hirschmann R, Hoffman JM, Phillips BT, Streeter KB. *J. Med. Chem.* 1982; **25**: 207–210.
11. Arya VP, Nagarajan K, Shenoy SJ. *Indian J. Chem., Sect. B* 1982; **21**: 941–944.
12. Nagarajan K, Arya VP, George T, Nair MD, Sudarsanam V, Ray DK, Shrivastava VB. *Indian J. Chem., Sect. B* 1984; **23**: 342–362.
13. Preiss M, Metzger KG. *Ger. Pat.* 2 658 906, 1978; *Chem. Abstr.* 1978; **89**: 146919.
14. Parmee ER, Naylor EM, Perkins L, Colandrea VJ, Ok HO, Candelori MC, Cascieri MA, Deng L, Feeney WP, Forrest MJ, Hom GH, MacIntyre DE, Miller RR, Stearns RA, Strader CD, Tota L, Wyvratt MJ, Fischer MH, Weber AE. *Bioorg. Med. Chem. Lett.* 1999; **9**: 749–754.
15. Naylor EM, Parmee ER, Colandrea VJ, Perkins L, Brockunier L, Candelori MC, Cascieri MA, Colwell LF Jr, Deng L, Feeney WP, Forrest MJ, Hom GH, MacIntyre DE, Strader CD, Tota L, Wang P, Wyvratt MJ, Fischer MH, Weber AE. *Bioorg. Med. Chem. Lett.* 1999; **9**: 755–758.
16. Reitz DB, Garland DJ, Olins GM, Makos CS, Gresk CJ, Litschgi JW, McKinnis BR. *Bioorg. Med. Chem. Lett.* 1994; **4**: 111–114.
17. Reitz DB, Garland DJ, Norton MB, Collins JT, Reinhard EM, Manning RE, Olins GM, Chen ST, Palomo MA, McMahon EG, Koehler KF. *Bioorg. Med. Chem. Lett.* 1999; **3**: 1055–1060.
18. Carling RW, Moore KW, Noyes CR, Jones EA, Bonner K, Emms F, Marwood R, Patel S, Patel S, Fletcher AE, Beer M, Sohal B, Pike A, Leeson PD. *J. Med. Chem.* 1999; **42**: 2706–2715.
19. Macías A, Dominguez A, Graupera N. *Pat. Cuba* 35 265, 1982.
20. Dago MA, Simonov EA, Pobedimskaya EA, Macías A, Martin A. *Kristallografiya* 1988; **33**: 1021–1023.
21. Johnson CK. *ORTEP-II. A Fortran Thermal-Ellipsoid Plot Program.* Report ORNL-5138. Oak Ridge National Laboratory: Oak Ridge, TN, 1976.
22. Lee C, Korp JD, Kohn H. *J. Org. Chem.* 1989; **54**: 3077–3083.
23. Svartman EL, Caram JA, Mirífico MV, Vasini EJ. *Can. J. Chem.* 1999; **77**: 511–517.
24. Caram JA, Mirífico MV, Vasini EJ. *Electrochim. Acta* 1994; **39**: 939–945.
25. Wright JB. *J. Org. Chem.* 1964; **29**: 1905–1909.
26. Riddick JA, Bunger WB. In *Techniques of Chemistry*, vol. 2, Weissberger A (ed). Wiley–Interscience: New York, 1970; 201.
27. Perrin DD, Armarego WLF. *Purification of Laboratory Chemicals*. Pergamon Press: Oxford, 1988.
28. Coetzee JF. *Recommended Methods for Purification of Solvents and Tests for Impurities*. Pergamon Press: Oxford, 1982.
29. Harms K, Wocadlo S. *XCAD4-CAD4 Data Reduction*. University of Marburg: Marburg, 1995.
30. Otwinowski Z, Minor W. *Methods Enzymol.* 1997; **276**: 307–326.
31. Sheldrick GM. *SHELXS-97. Program for Crystal Structure Resolution*. University of Göttingen: Göttingen, 1997.
32. Sheldrick GM. *SHELXL-97. Program for Crystal Structures Analysis*. University of Göttingen: Göttingen, 1997.

