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Reactions of the activated, rigid, α-diazomethine group of 1,2,5-thiadiazole 1,1-dioxides with nitrogenated nucleophiles. Part III: aliphatic monoamines and phenylhydrazine

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ABSTRACT: The reactions of *n*-butylamine ($BuNH_2$), 2-aminoethanol ($H_2N(CH_2)_2OH$), diethylamine (Et_2NH), and phenylhydrazine (PhN_2H_3) with 3,4-diphenyl-(**1a**) and phenanthro[9,10-c]-1,2,5-thiadiazole 1,1-dioxide (**1b**) were studied by cyclic voltammetry (CV) and ^{1}H- and ^{13}C-NMR in aprotic solvent solution. The course of the reactions depended on the substrate-nucleophile combination: Et_2NH added to **1a** or **1b**, forming the corresponding thiadiazolines in an equilibrium monoaddition reaction. The equilibrium constants were evaluated and compared. With primary amines and PhN_2H_3, the nucleophile added to both C═N double bonds of **1a** and displaced the sulfamide moiety. In the case of the reaction of **1a** with PhN_2H_3, the intermediate monoaddition thiadiazoline, 3-(2-phenylhydrazino)-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide, was also isolated. $BuNH_2$ and $H_2N(CH_2)_2OH$ reacted with **1a** to give α-bis-imines, while **1a** with PhN_2H_3 gave the α-bis-hydrazone. The configurations of benzil bis(ethanolimine) and benzilosazone were determined by single crystal x-ray diffraction analysis as Z,Z. $BuNH_2$ and PhN_2H_3 reduced **1b** to the corresponding thiadiazoline compound **1b**H_2. Copyright © 2006 John Wiley & Sons, Ltd.

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KEYWORDS: 1,2,5-thiadiazole 1,1-dioxide; nucleophilic addition; monoamines; benzilimines; benzilosazone

INTRODUCTION

The reactants and products discussed in this work (with the exception of **1b**H_2, Fig. 8) are summarized in Scheme 1.

In recent papers, we reported the addition reaction of several nucleophiles (alcohols, thiols, aromatic monoamines, and monocarboxamides)[1–5] to the C═N double bonds of 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides. Only equilibrium monoaddition reactions to give **1a**. XH compounds (Scheme 1) were observed. Coherently, these nucleophiles do not react with 1,2,5-thiadiazoline 1,1-dioxides.

However, bifunctional nitrogen nucleophiles such as ureas and thioureas, add to both C═N double bonds of some 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides yielding bicyclic compounds (Fig. 1). The stability acquired by cycle formation and the intramolecular character of the second addition might justify the increased reactivity.[6]

We report here the reactions of aliphatic monoamines: *n*-butylamine ($BuNH_2$), diethylamine (Et_2NH), and 2-aminoethanol ($H_2N(CH_2)_2OH$), and of phenylhydrazine (PhN_2H_3) with 3,4-diphenyl-(**1a**) and phenanthro[9,10-c]-1,2,5-thiadiazole 1,1-dioxide (**1b**) in aprotic solvent solution. The reacting systems were followed using cyclic voltammetry (CV) and ^{1}H- and ^{13}C-NMR. Our CV method[2,4] was used to evaluate the equilibrium constants of the reactions of **1a** and **1b** with Et_2NH.

EXPERIMENTAL

Compounds **1a**, **b** were synthesized according to Wright.[7] Standard methods[8–10] were used for purification of commercial solvents and nucleophiles. The solvents were

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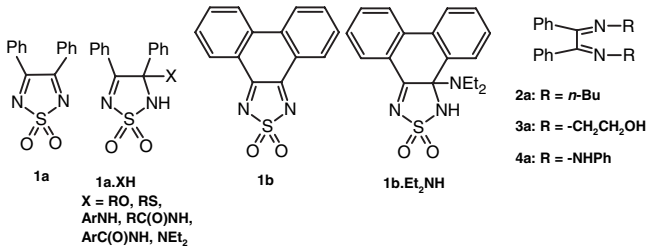


Scheme 1

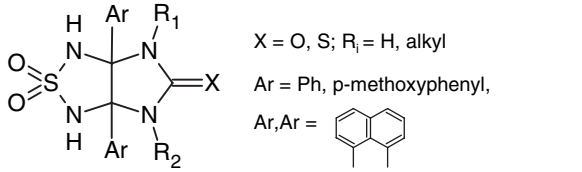


Figure 1. Products of the addition of bifunctional nitrogen nucleophiles to the indicated **1a** derivatives

dried with molecular sieves and stored under a dry nitrogen atmosphere in a glove box. Their water content (*ca* 50 ppm) was measured by Karl–Fischer coulometric titration.

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

The 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 Teflon, the counter-electrode was a 2 cm^2 Pt foil and a Ag^+ (0.1 M, MeCN)/Ag reference electrode (to which all potentials reported are referred) was used. The supporting electrolyte was 0.1 M $NaClO_4$. A LYP-M2 potentiostat, a 3-module LYP sweep generator and a Houston Omnigraphic 2000 pen recorder were used. The preparation of solutions, the CV experiments and other manipulations were made in a glove box under a dry nitrogen atmosphere.

Single crystal x-ray data of **3a** were collected with COLLECT[11] program on a KappaCCD diffractometer, using φ and ω scans. The data were reduced with DENZO and SCALEPACK.[12] A complete data set for **4a** was collected with EXPRESS[13] on an Enraf-Nonius CAD-4 diffractometer, using the ω-2ϑ scan technique. The data were reduced with XCAD4.[14] A graphite monochromated MoKα radiation ($\lambda = 1.54184$ Å) was used in both cases. The experimental ranges were 3.15–25.00° (**3a**), and 3.86–67.87° (**4a**).

The structures were solved by direct and Fourier methods with SHELXS-97[15] and the non-H atoms in the final molecular model were refined anisotropically by full-matrix least-squares on F^2 employing SHELXL-97.[16]

All hydrogen atoms were found in a difference Fourier map. However, they were positioned stereochemically and refined with the riding model. The positions of the HO-hydrogen atoms in **3a** were optimized by allowing them to rotate around the corresponding C—O bond. The molecular plots of compounds **3a** (Fig. 3) and **4a** (Fig. 6) were drawn with ORTEP.[17]

Single crystals for x-ray data were obtained by slow evaporation of the solvent from ethanol solutions of the compounds.

N-[1,2-diphenyl-2-(butylimino)ethylidene]butylamine (benzil bis (*n*-butylimine) (2a)

One hundred twenty three milligrams (0.46 mmol) of **1a**, and 71 mg (0.97 mmol) of $BuNH_2$ were dissolved in anhydrous MeCN (6 ml) and kept tightly closed and protected from light. Two months later the solvent was removed by rotary evaporation at room temperature. The residue was extracted three times with 1 ml of CH_2Cl_2. The remaining white solid was filtered, dried (40 mg, 0.42 mmol) and identified as sulfamide through its IR spectrum. Evaporation at reduced pressure and room temperature of the CH_2Cl_2 solvent gave the product (130 mg, 89%) as a colorless unstable liquid, which turned gradually yellow.

^{1}*H-NMR* (δ, TMS) in MeCN-d_3: 7.72–7.32 (2Ph, 16 signals, 10H), 3.32–3.26 (=N—C**H$_2$**—, multiplet, 4H), 1.69–1.58 (=N—CH_2—C**H$_2$**—, multiplet, 4H), 1.44–1.29 (=N—CH_2—CH_2—C**H$_2$**—, multiplet, 4H), and 0.88–0.83 (=N—CH_2—CH_2—CH_2—C**H$_3$**, triplet, 6H).

^{13}*C-NMR* (δ, TMS) (same solution): 165.5 (**C**=N), 137.0–127.8 (2Ph, 4 signals), 54.7 (=N—**C**H_2—), 33.7 (=N—CH_2—**C**H_2—), 21.4 (=N—CH_2—CH_2—**C**H_2—), and 14.2 (=N—CH_2—CH_2—CH_2—**C**H_3).

IR (film; cm^{-1}): 3015 (C_{Ar}—H), 2990–2980 (C_{Aliph}—H), 1625 (C=N), 1590 (Ar), 1575 (Ar), 1485, 1450, 1370, 1350, 1310, 1280, 1230, 1175, 1025, 925, 900, 770, and 695.

Anal. Calcd for $C_{22}H_{28}N_2$: C, 82.45; H, 8.81; N, 8.74. Found: C, 84.09; H, 8.69; N, 9.15, S, 0.00%.

2-({(1Z,2Z)-2-[(2-hydroxyethyl)imino]-1,2-diphenylethylidene}amino) ethanol (benzil bis(ethanolimine)) (3a)

Two hundred twenty milligrams (0.82 mmol) of **1a** and 187 mg (3.06 mmol) of $H_2N(CH_2)_2OH$ were dissolved in anhydrous MeCN (1.7 ml). Twenty days after solution preparation, the solvent was removed by rotary evaporation at room temperature. The residue was extracted three times with CH_2Cl_2 (total volume: 5 ml). A white solid remained and was identified as sulfamide. The CH_2Cl_2 solution was dried with anhydrous Na_2SO_4, concentrated by evaporation at reduced pressure, and cooled overnight. The solid obtained was filtered, recrystallized from hot CH_2Cl_2 and dried under vacuum at room temperature. Yield: 172 mg, 0.58 mmol (71%).

The Z,Z configuration of the compound was determined by x-ray diffraction analysis (Fig. 3).

^{1}*H-NMR* (δ, TMS) in DMSO-d_6: 7.70–7.37 (2Ph, 9 signals, 10H), 5.76 (O**H**), 4.69–4.65 (=N—C**H$_2$**—,

triplet, 4H), 3.72–3.00 (=N—CH_2—C**H_2**—OH, broad doublet, 4H).

^{13}*C-NMR* (δ, TMS) (same solution): 165.0 (**C**=N), 135.2–126.8 (2Ph, 4 signals), 61.1 (=N—**C**H_2—), 56.5 (=N—CH_2—**C**H_2—OH).

IR (KBr, cm^{-1}): 3250 (OH), 3010 (C_{Ar}—H), 2980 (C_{Aliph}—H), 1620 (C=N), 1560 (Ar), 1495, 1450, 1400, 1260, 1220, 1205, 1170, 1050, 930, 850, 770, and 680.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45; O: 10.80. Found: C, 73.26; H, 6.78; N, 9.97, S, 0.00%.

Crystal dimensions $0.14 \times 0.28 \times 0.34$ mm, orthorhombic, Pbca, $a = 9.3075(1)$ Å, $b = 11.1683(3)$ Å, $c = 30.5917(7)$ Å, $V = 3180.0(1)$ Å^3, $Z = 8$, ρcalc = $1.238\ g \cdot cm^{-3}$, 21801 reflections measured, 2686 independent [R(int) = 0.0442], $R1 = 0.0666$ [2145 reflections with $I > 2\sigma(I)$], wR2 = 0.1842, 201 parameters, residual electron density 0.291/−0.314 e.Å^{-3}. Crystallographic data for the structure of **3a** were deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC: 290220.

(1Z,2Z)-1,2-diphenylethane-1,2-dione bis(phenylhydrazone) (benzilosazone) (4a) and 3-(2-phenylhydrazino)-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (1a.PhN_2H_3)

4a: 140 mg (0.52 mmol) of **1a** and 125 mg (1.16 mmol) PhN_2H_3 were dissolved in anhydrous MeCN (1.0 ml). A yellow colored solid precipitated immediately after solution preparation. The filtered solid, combined with that obtained by concentration at room temperature of the mother liquors (1/10), was dried under vacuum at room temperature and recrystallized from hot ethanol. One hundred fifty milligrams (0.39 mmol; 74%) of the pure (TLC) product mp: 234–236 °C were obtained. It was identified as the 1Z,2Z isomer by x-ray diffraction. Crystallographic data for the structure of **4a** were deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 290219.

^{1}*H-NMR* (δ, TMS) in DMSO-d_6: 9.58 (PhN**H**-, 1 signal, 2H), 7.62–6.77 (2Ph, 15 signals, 20H).

^{13}*C-NMR* (δ, TMS) (same solution): 153.5 (**C**=N), 144.9–113.3 (2Ph, 10 signals).

IR (KBr, cm^{-1}): 3306 (N—H), 3020 (C_{Ar}—H), 1598 (C=N), 1577 (Ar), 1535, 1504 and 1488, 1452, 1305, 1248, 1163 and 1142, 1066, 740 and 679.

Crystal dimensions $0.10 \times 0.10 \times 0.22$ mm, tetragonal, I41/a, $a = b = 16.441(3)$ Å, $c = 15.936(6)$ Å, $V = 4308(2)$ Å^3, $Z = 8$, ρcalc = $1.204\ g \cdot cm^{-3}$, 2232 reflections measured, 1929 independent [R(int) = 0.0309], $R1 = 0.0491$ [1076 reflections with $I > 2\sigma(I)$], wR2 = 0.1207, 148 parameters, residual electron density 0.151/−0.141 e.Å^{-3}.

1a.PhN_2H_3: In a separate synthesis, only the filtered solid was worked-up: it was, washed with MeCN, H_2O, EtOH (50:50) and EtOH, and dried under vacuum at 60 °C. The solid was identified as the thiadiazoline **1a.**PhN_2H_3, (i.e., a thiadiazoline as those represented in Scheme 1 as **1a**.XH, with X: PhN_2H_2), mp 130–131 °C (dec). The identification was based on its IR, ^{1}H- and ^{13}C-RMN spectra and CV behavior and the comparison of these results with those of numerous thiadiazolines derived from **1a** synthesized in our laboratory[4,5,18] or reported in the literature.[19] As it also happened with many of those thiadiazolines, recrystallization attempts from hot EtOH or MeCN produced only **1a**, presumably because the addition is an equilibrium reaction and **1a** is less soluble than the addition product **1a**.PhN_2H_3.

^{1}*H-NMR* (δ, TMS) in DMSO-d_6: 9.01 (O_2S—N**H**, 1 signal), 8.07–6.34 (2Ph, 20 signals).

^{13}*C-NMR* (δ, TMS) (same solution): 177.5 (**C**=N), 145.4–114.6 (2Ph, 12 signals), 91.0 (Ph**C**NH).

IR (KBr, cm^{-1}): 3250 (N—H), 3209 (N—H), 3066 (C_{Ar}—H), 1605 and 1590 (Ar), 1561 (C=N), 1498, 1446, 1357, 1320 (>SO_2), 1279, 1255, 1215, 1180 (>SO_2), 1117, 1039, 973, 907, 871, 818, 760, and 690.

Phenanthro [9,10-c]-1,2,5-thiadiazoline 1,1-dioxide (1bH_2)

One hundred eighteen milligrams (0.44 mmol) **1b** and 163 mg (1.51 mmol) PhN_2H_3 were dissolved in anhydrous MeCN (1.0 ml). A light yellow colored solid precipitated after one day. The solid was filtered, washed with toluene, and dried under vacuum at room temperature. One hundred milligrams (86%) of the pure product was obtained. It was identified by its IR spectrum, mixed melting point and CV, as compared with an authentic sample.[20] **1b** was also reduced to **1b**H_2 (Fig. 8) by $BuNH_2$, as observed by CV. This reaction was not further investigated.

RESULTS AND DISCUSSION

A summary of the reactions of **1a** and **1b** studied in this work is given in Table 1.

Reactions with primary aliphatic amines

Reaction of 1a with $BuNH_2$. Only one symmetric isomer of the benzil bis(*n*-butylimine) **2a** was obtained, as indicated by the single ^{13}C-NMR signal at 165.5 ppm assigned to **C**=N. No further studies to decide if the product was the E,E or the Z,Z isomer were possible because the substance was an unstable liquid (Experimental). The E,E configuration is proposed as the most stable for benzilosazones according to published

Table 1. Summary of studied reactions

Substrate	Nucleophile	Products
1a	$BuNH_2$	Benzil bis(*n*-butylimine) (**2a**)
1b	$BuNH_2$	**1b**.H_2
1a	$H_2N(CH_2)_2OH$	Benzil bis(ethanolimine) (**3a**)
1a	Et_2NH	**1a**.Et_2NH (equilibrium reaction)
1b	Et_2NH	**1b**.Et_2NH (equilibrium reaction)
1a	PhN_2H_3	Benzilosazone (**4a**) (intermediate product: **1a**.PhN_2H_3)
1b	PhN_2H_3	**1b**H_2

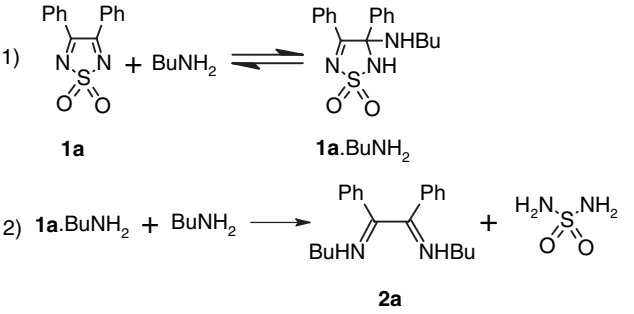
studies,[21] while for monoimines the relative stability of the E or Z configuration depends on the substituent groups.[22] As reported in the experimental part and discussed below, a Z,Z configuration was found for benzil bis(ethanolimine) (**3a**) and benzilosazone (**4a**).

Some insight on the reaction steps was obtained from the ^{13}C-, ^{1}H-NMR spectra and CVs scanned during its course. The ^{13}C-NMR spectra of a solution of **1a** and $BuNH_2$ in MeCN-d_3, in a 1:1 molar ratio, showed, 2 h after solution preparation, signals assigned to the sp^2 and the sp^3 (178.0 and 90.9 ppm, respectively) heterocyclic C-atoms of **1a**.$BuNH_2$ (Scheme 2). The resonances of the *n*-butyl radical of **1a**.$BuNH_2$ (43.0, 32.2, 20.9, and 14.0 ppm) were also observed. One week later, the signals at 178.0 and 90.9 ppm remained, but a new signal at 165.5 ppm, which was assigned to the (equivalent) sp^2 C-atoms of the benzil bis(*n*-butylimine) **2a** was also present. The *n*-butyl radical signals were observed at 54.6, 33.6, 21.2, and 14.0 ppm. Some signals corresponding to **1a**.$BuNH_2$ were still observable, but disappeared completely in the spectrum scanned 45 days after solution preparation, which showed only the **2a** signals.

^{1}H-NMR spectra of the same solution were scanned 2 h, 1 week, and 45 days after solution preparation. When compared with the ^{1}H-NMR spectra of $BuNH_2$ and **2a** in the same solvent, it was observed that the methyl protons of the *n*-butyl radical remained approximately at the same position (δ *ca* 0.85 ppm), while the complex signal of the $CH_3C\mathbf{H_2}C\mathbf{H_2}$— protons of the $BuNH_2$ (1.37–1.30 ppm) splitted into two downfield shifted groups (1.69–1.58 ppm, 10 signals and 1.44–1.29 ppm, 9 signals) in the 45 days spectrum. A new signal at *ca* 3.3 ppm, assigned to the $=NC\mathbf{H_2}$ of **2a**, appeared in the 1-week spectrum. The 45 days spectrum presented all signals of **2a** (Experimental) along with other signals probably arising from remaining **1a**.$BuNH_2$ and sulfamide.

The initially clear and homogeneous solution in the NMR tubes presented, at the end of these experiments, a white solid precipitate, which was identified as **1a**.

To study further this re-precipitation phenomenon, a very concentrated 1:1 molar ratio solution was prepared: $BuNH_2$ (0.46 mmol) was added to a suspension of **1a** (0.46 mmol) in 1 ml of anhydrous MeCN (**1a** is only slightly soluble in MeCN). Upon amine addition, **1a**



Scheme 2

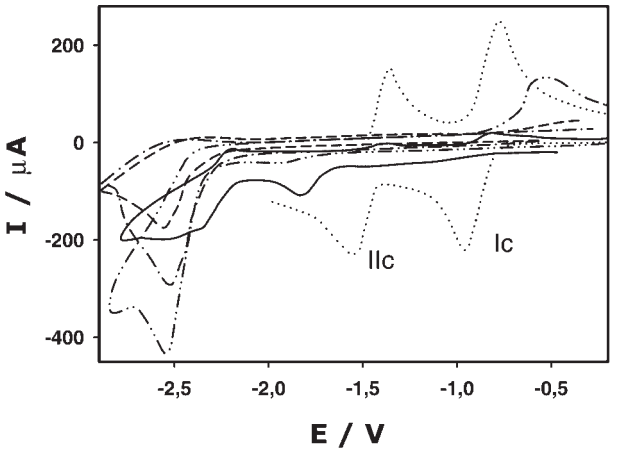


Figure 2. Time evolution of the CVs of the **1a**/$BuNH_2$ system. Scan rate: 0.2 Vs^{-1}. **1a**: 7.00 mM; $BuNH_2$: 33.0 mM. Scanned solutions were prepared by dilution (with 0.1 M $NaClO_4$, DMF) of a stock **1a**-$BuNH_2$-DMF solution, as detailed in the text. CV of **1a** (7.30 mM in DMF, dotted line) is included for reference. (—): CV scanned immediately after stock solution preparation ($t = 0$), (**- - -**): $t = 8$ days, (- · -): $t = 34$ days, (**- · · -**): CV of a 7.95 mM **2a** solution in 0.1 M $NaClO_4$, DMF

dissolved immediately and completely, however, as it happened in the NMR experiments, a white precipitate, identified as **1a**, was observed after a couple of hours. It was concluded from these observations that reaction 1 (Scheme 2) was a rapid equilibrium reaction, with a relatively high equilibrium constant. Thus, the fresh solution of **1a** and $BuNH_2$ in 1:1 molar ratio should contain almost exclusively the thiadiazoline **1a**.$BuNH_2$. The remaining $BuNH_2$, in a low equilibrium concentration, would slowly react with **1a**.$BuNH_2$ forming **2a** (Eqn (2), scheme 2). Since the global reaction is

$$\mathbf{1a} + 2\ BuNH_2 \rightarrow \mathbf{2a} + SO_2(NH_2)_2,$$

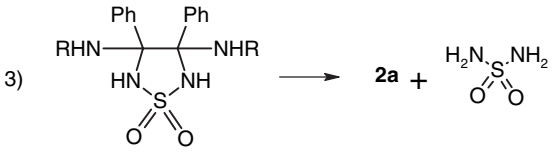
1a is in excess at a molar ratio [**1a**]/[$BuNH_2$] = 1, and, owing to its low solubility, should precipitate. The reprecipitation of **1a** was not observed in similar tests with higher amine concentrations ([**1a**]/[$BuNH_2$] molar ratios less than 0.5). The reaction was also followed by CV (Fig. 2). A stock solution of **1a** (0.74 mmol) and $BuNH_2$ (3.79 mmol) in MeCN (1.9 ml) was prepared. At

selected times, 20–30 μl of the stock solution were diluted with 1–2 ml of DMF (containing 0.1 M $NaClO_4$ as supporting electrolyte), and a CV was scanned immediately thereafter.

A CV was registered as soon as the stock solution was prepared. The characteristic CV couples of **1a** were not present. Three cathodic peaks (−1.83, −2.40 (shoulder), and −2.56 V); were observed instead. The peak at −2.56 V corresponds to **2a**, as concluded by comparison with the CV of an authentic sample of the compound. Peaks at −1.83 and −2.40 V are similar to those found for 1,2,5-thiadiazoline 1,1-dioxides,[4–6] and were assigned to **1a**.$BuNH_2$ (Eqn (1), Scheme 2).

Only the peak at −2.56 V was observed in the CV registered at a reaction time $t = 8$ days. CVs registered at intermediate times (not shown) revealed a continuous decrease in the current intensity of the thiadiazoline peaks and an increase of the peak at −2.56 V.

It was also observed that the current intensity of the −2.56 V signal continued to increase even after the disappearance of the thiadiazoline peaks (see 34 days CV, Fig. 2), reaching a level that remained constant in time. This behavior suggested the presence of a nonelectroreducible intermediate that decomposed to give **2a**. A 3,4-*n*-butylamino disubstituted thiadiazolidine might be this intermediate, as we have observed that thiadiazolidine compounds do not present voltammetric electroreduction signals in the experimental potential range used.[6] If this were the case, **2a** would be formed by the separation of a sulfamide molecule from the intermediate, as indicated in Eqn (3).



Reaction of 1b with $BuNH_2$. Compound **1b** was reduced to **1b**H_2 by $BuNH_2$ as well as by PhN_2H_3 (see below 'reactions of **1b** with PhN_2H_3,'), but a separate synthesis of **1b**H_2 from **1b** and $BuNH_2$ was not attempted. The reduction product was only identified in the final CV of the reaction mixture, which was coincident with that found for the **1b**/PhN_2H_3 system and with the CV of a sample of **1b**H_2.[20]

Reaction of 1a with $H_2N(CH_2)_2OH$. Stereoselective synthesis of 2-({(1Z,2Z)-2-[(2-hydroxyethyl)imino]-1,2-diphenylethylidene} amino) ethanol (benzil bis(ethanolimine)) (3a). The reaction of **1a** with $H_2N(CH_2)_2OH$ in MeCN solution gave a white solid identified as the 1Z,2Z isomer of **3a**. Figure 3 shows a molecular diagram of this isomer as determined by single crystal x-ray diffraction.

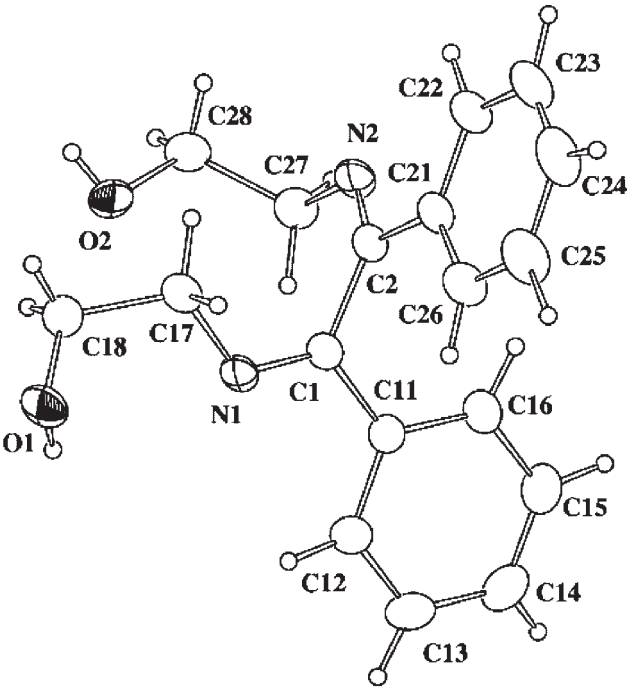


Figure 3. Molecular diagram of **3a** showing the labeling of the non-H atoms and their displacement ellipsoids at the 30% probability level

The ^{13}C-NMR spectrum of **3a** showed only four signals for both phenyl rings, one signal for both sp^2 C-atoms and two signals for the sp^3 C-atoms, thus confirming the presence of only one symmetric isomer in solution.

The time evolution of the CVs of the reacting system, followed using the same procedure detailed above for the reaction of **1a** with $BuNH_2$, is shown in Fig. 4.

An initial CV did not show the **1a** couples. Three cathodic peaks (−1.87, −2.38 (shoulder), and −2.50 V) were observed instead. Their current intensities changed with time and after 60 days only the peak at −2.38 V remained. The peaks at −1.87 and −2.50 V were assigned to the thiadiazoline **1a**.$H_2N(CH_2)_2OH$. The peak at −2.38 V corresponded to **3a** by comparison with the CV of an authentic sample of the compound (Experimental).

Unlike the case of the **1a**/$BuNH_2$ system, the voltammetric peak of **3a** reached its highest current intensity simultaneously with the disappearance of the peaks of the thiadiazoline intermediate **1a**.$H_2N(CH_2)_2OH$. Therefore, if the reactions paths were similar, the decomposition of the intermediate (reaction 3) must be faster. Apparently neighboring group (HO) participation must be operating.

Reactions with secondary aliphatic amines: equilibrium systems

Reactions of 1a and 1b with Et_2NH. These reactions were studied using CV. A typical experiment consisted in the addition of Et_2NH (to obtain an initial concentration in the 0.1–2.7 M concentration range) to a solution of **1a**

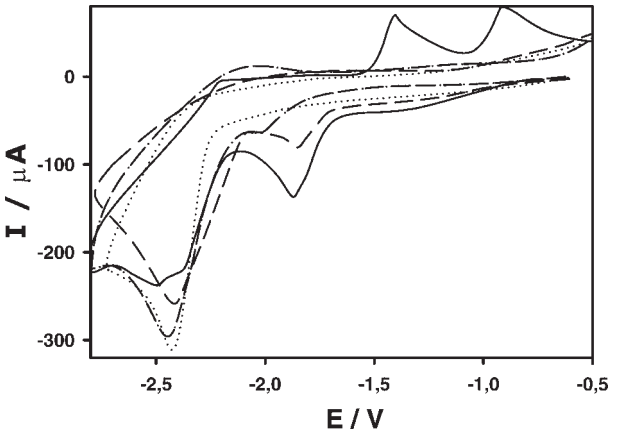


Figure 4. Time evolution of the CVs of the **1a**/$H_2N(CH_2)_2OH$ system. Scan rate: 0.2 Vs^{-1}, **1a**: 7.16 mM; $H_2N(CH_2)_2OH$: 0.143 M. Solutions prepared by dilution of a stock, as indicated in the text. (—): CV scanned immediately after stock solution preparation ($t = 0$), (**- - -**): $t = 10$ days, (- · -): $t = 60$ days, (· · ·): CV of a 6.12 mM **3a** solution in 0.1 M $NaClO_4$, DMF

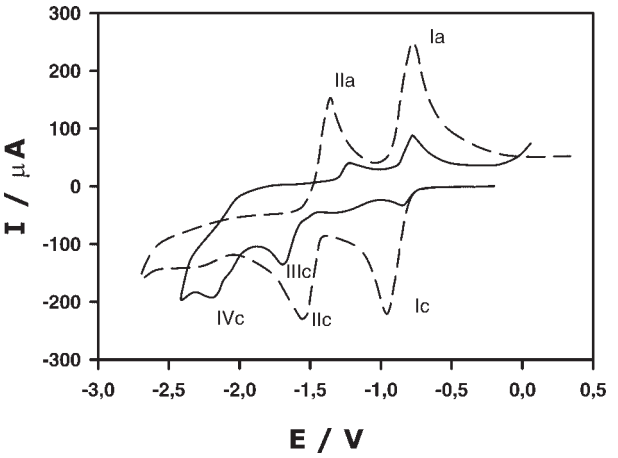
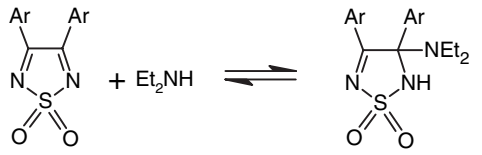


Figure 5. CVs of the **1a**/Et_2NH system. Scan rate: 0.2 Vs^{-1}. (**- - -**): CV of a 7.30 mM solution of **1a**; (—) equilibrium CV of the same solution after addition of Et_2NH to a 0.29 M final concentration. DMF solvent, supporting electrolyte: 0.1 M $NaClO_4$

or **1b** (*ca* 6 mM) in DMF solvent, with 0.1 M $NaClO_4$ as supporting electrolyte. CVs of the solutions were registered initially and at convenient times during the course of the reactions.

The rate of change of the CV signals increased with the increase in the concentration of added Et_2NH, and a final equilibrium CV was obtained in all cases. The changes, as below described and shown in Fig. 5 for **1a**/Et_2NH system, followed a well-known sequence, already reported by us when the mono-addition of alcohols[3,4] or amides[5,6] were studied. Therefore, we concluded that the reactions corresponded to the mono-addition of Et_2NH to **1a** or **1b** (reaction 4).

4) 

The CV changes observed were the following: the current intensity of both cathodic peaks of the thiadiazole (Ic and IIc) decreased simultaneously. Peak IIc disappeared from the final equilibrium CV for all experimental Et_2NH nucleophile concentrations used, but the current intensity of peak Ic decreased and reached a final equilibrium intensity that was inversely proportional to the nucleophile concentration. Two cathodic peaks (IIIc and IVc) at more negative potentials appeared and increased in current successively: peak IVc, when peak IIc started to decrease, and peak IIIc, after the disappearance of peak IIc.

As already discussed,[2,4] these changes are coherent with the following mechanism, illustrated for **1a**: in the equilibrium CV, equal quantities of **1a** and of the addition thiadiazoline **1a**.Et_2NH are consumed at peak Ic by the reactions:

$$\text{E1} \quad \mathbf{1a} + e^- \Leftrightarrow \mathbf{1a}^{\cdot -}$$
$$\text{C1} \quad \mathbf{1a}^{\cdot -} + \mathbf{1a}.Et_2NH \Leftrightarrow \mathbf{1a}H^{\cdot} + \mathbf{1a}.Et_2NH^-$$
$$\text{E2} \quad \mathbf{1a}H^{\cdot} + e^- \Leftrightarrow \mathbf{1a}H^-$$

Thus, peak IIc, associated with the electroreduction of $\mathbf{1a}^{\cdot -}$ to $\mathbf{1a}^{2-}$, is no longer present (under the experimental conditions chosen, see below) because $\mathbf{1a}^{\cdot -}$ is completely consumed by reaction C1. Cathodic peak IIIc is associated with the electroreduction of the addition thiadiazoline that has not been consumed at peak Ic by reaction C1:

$$\text{E3} \quad \mathbf{1a}.Et_2NH + e^- \Leftrightarrow \mathbf{1a}.Et_2NH^{\cdot -}$$
$$\text{C2} \quad \mathbf{1a}.Et_2NH^{\cdot -} \Leftrightarrow \mathbf{1a}.H^{\cdot} + Et_2NH^{\cdot -}$$

followed immediately by the electroreduction of $\mathbf{1a}H^{\cdot}$ to $\mathbf{1a}H^-$ (E2). The anions $\mathbf{1a}H^-$ and **1a**.Et_2NH^- are further reduced at peak IVc.

In the presence of a sufficient excess of the nucleophile (i.e., $[Et_2NH]_{equilibrium} \approx [Et_2NH]_0$), and if peak IIc is absent from the equilibrium CV (i.e., peak Ic corresponds to the E1C1E2 mechanism above), a function of the current intensity of peaks Ic and IIIc in the equilibrium CV and the voltage sweep rate (ν), (Eqn (5)),[2,4] can be used to estimate the equilibrium constant of the addition reaction.

$$K \times [\mathrm{Nu}]_0 = \frac{2 \times \left\{ \frac{i(\mathrm{IIIc})}{\nu^{1/2}} + \frac{i(\mathrm{Ic})}{2 \times \nu^{1/2}} \right\}}{\frac{i(\mathrm{Ic})}{\nu^{1/2}}} \qquad (5)$$

where $[Nu]_0$ is the initial Et_2NH concentration, and K is the equilibrium constant of reaction 4.

The linear dependence of the peak current intensity of Ic and IIIc with $\nu^{1/2}$, a requisite for the validity of Eqn (5), was verified for these systems in the range of experi-

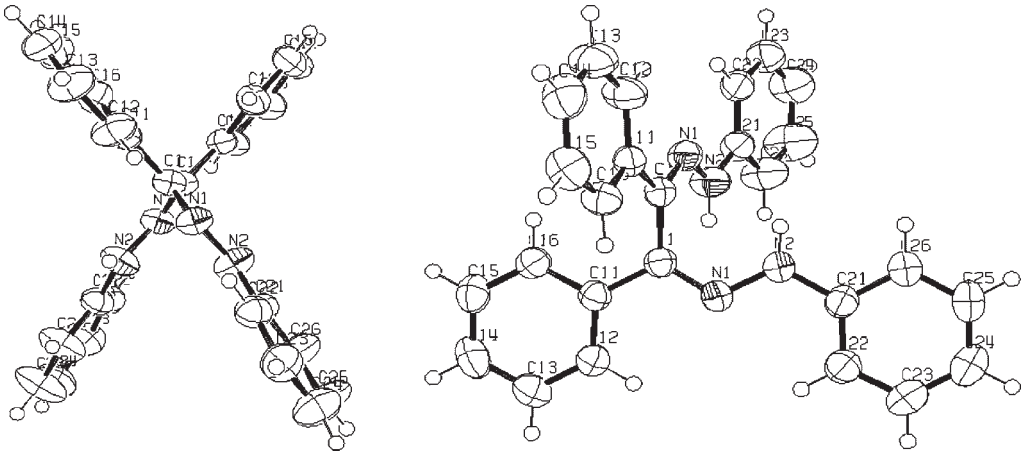


Figure 6. Different views of the ORTEP diagram of **4a**. The view on the left shows that one half of the molecule is symmetry related the other half through a crystallographic two-fold axis

mental sweep rates (0.05–0.30 Vs^{-1}). The estimated equilibrium constants were 23 ± 2 and $3.6 \pm 0.5\ M^{-1}$ for the formation of **1a**.Et_2NH and **1b**.Et_2NH, respectively.

The relatively smaller equilibrium constant for **1b**.Et_2NH might be related to the molecular geometry of the parent thiadiazole.[23] In **1b**, the —N═C—C═N— group is in the plane of the aromatic system and the C═N double bonds participate of the delocalized electronic system. Thus, the formation of the **1b**.Et_2NH thiadiazoline not only involves the opening of the C═N double bond, but also decreases the extent of this resonance system. This does not happen in the case of **1a**, for their phenyl rings are out (by *ca* 42°) of the heterocyclic plane and only weakly conjugated with the C═N bonds.[24]

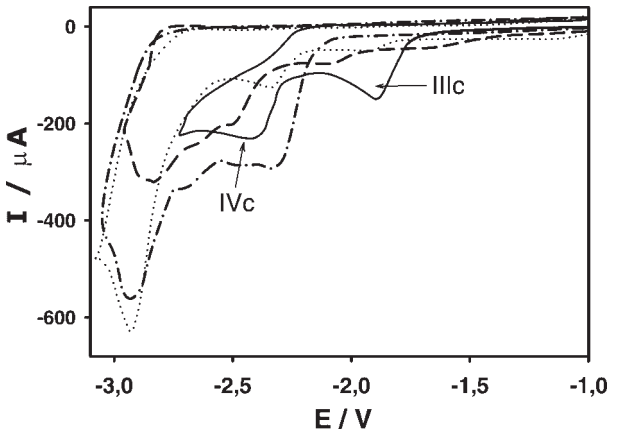


Figure 7. Time evolution of the CVs of the **1a**/PhN_2H_3 system. Scan rate: 0.2 Vs^{-1}. **1a**: 7.83 mM; PhN_2H_3: 19.0 mM. Scanned solutions were prepared by dilution (with 0.1 M $NaClO_4$, DMF) of a stock **1a**-PhN_2H_3-DMF solution, as detailed in the text. (—): CV scanned immediately after stock solution preparation ($t = 0$), (**- - -**): $t = 48$ h, (- · -): $t = 364$ h, (· · ·): CV of a 7.51 mM **4a** solution in 0.1 M $NaClO_4$, DMF

Reaction with PhN_2H_3

Reaction of 1a with PhN_2H_3. **1a** reacted with PhN_2H_3 in MeCN solution yielding **4a** (Experimental).

Only one ^{13}C-NMR signal assigned to **C**═N (at 153.5 ppm) was observed. This indicated that a symmetrical isomer was obtained. Single crystal x-ray diffraction showed the Z,Z isomer. Figure 6 shows its highly symmetric structure, with the phenyl rings arranged in a tetrahedral geometry.

The reaction was followed by the changes in the CVs of the reacting solution. A stock solution of **1a** and PhN_2H_3 (**1a**: 0.59 mmol; 0.293 M; PhN_2H_3: 1.42 mmol; 0.713 M; DMF: 2.0 ml, supporting electrolyte: 0.1 M $NaClO_4$) was prepared. At selected times, 50 μl of the stock solution were diluted with 1.6 ml of DMF (containing 0.1 M $NaClO_4$ as supporting electrolyte), and a CV scan was registered immediately thereafter.

The resulting CVs are shown in Fig. 7. The changes with time were similar to those observed in the **1a**-$BuNH_2$-MeCN system described above: the initial CV, scanned immediately after PhN_2H_3 addition, did not show **1a** peaks Ic and IIc, but two irreversible signals (IIIc: −1.90 V, IVc: −2.45 V), assigned to the thiadiazoline **1a**.XH (Scheme 1 with $X = PhN_2H_2$) initially formed by the fast nucleophilic monoaddition of PhN_2H_3 to **1a**. As the reaction proceeded, the thiadiazoline voltammetric signals decreased gradually and after 390 min an almost featureless (only a very low intensity peak is observed at −2.45 V) CV was registered. Finally, peaks at −2.40 and −2.90 V appeared and increased with time. The CV remained unchanged thereafter. The final CV corresponds with that of an authentic benzilosazone sample. The reaction mechanism, judging by the similarity of the CV responses, might be that proposed above for the reaction of **1a** with $BuNH_2$.

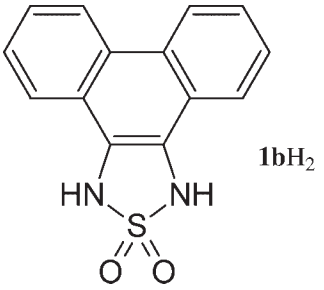


Figure 8. **1b**H_2:phenanthro[9-10-c]-1,2,5-thiadiazoline1, 1-dioxide

The CV detected intermediate thiadiazoline **1a**.PhN_2H_3 (**1a**.XH; Scheme 1 with X = PhN_2H_2) was isolated in a synthetic assay performed in similar conditions (Experimental).

Reaction of 1b with PhN_2H_3. **1b** reacted with PhN_2H_3 yielding the reduction product **1b**H_2, which was identified by its IR spectrum, mixed melting point and CV, as compared with an authentic sample.[20] **1b**H_2 was also obtained in the reaction of **1b** with $BuNH_2$, as above mentioned.

The differences between the reactions of **1a** and **1b** with these nucleophiles can be related to the structure of the substrates. The thiadiazole heterocycle in **1b** is substituted at the 3,4 positions by a connected π-system which is in the same plane of the heterocycle.[23] This allows the inclusion of the two C═N double bonds in an extended delocalized π-system. Also, as we have observed,[6] thiadiazoline **1b**H_2 differs from the typical 1,2,5-thiadiazole structure, since both carbon–nitrogen bonds are single. In the formation of the thiadiazoline **1b**H_2, resonance stability is preserved by replacing the original delocalized system of **1b** by a phenanthrene group (Fig. 8).

On the contrary, in **1a** the plane of each phenyl ring is rotated out of the heterocyclic plane by *ca* 42° and their resonance coupling with the C═N bonds is weak.[24] In a hypothetical **1a**H_2, with the same structure of **1b**H_2, the C═C double bond would only worsen the steric repulsion between the phenyl rings by bringing them closer together without providing additional delocalization energy.

CONCLUSIONS

Primary aliphatic monoamines and phenylhydrazine reacted almost instantaneously with **1a**, to form the corresponding thiadiazolines, which were unstable in the reaction media. The reactions involved the initial, very fast, nucleophilic attack of the *N* atom of the nucleophile to only one of the identical electron-deficient heterocyclic carbon atom of the substrate. This initial thiadiazoline formation was observed by CV and NMR experiments, and, in the case of the **1a**/PhN_2H_3 system, the thiadiazoline was actually isolated. A rationale for the practical lack of diaddition of alcohol nucleophiles has been given,[4] based on the structure of **1a**[24] and its thiadiazoline derivatives.[25] However, the stronger nitrogen nucleophiles can react further, attacking the remaining >C═N- double bond of the substrate to yield thiadiazolidines.

The displacement of a sulfamide molecule gave the final reaction product. In the case of the $H_2N(CH_2)_2OH$ nucleophile the departure of the leaving group was easier than for $BuNH_2$ or PhN_2H_3. This suggests an influence of the HO neighboring group in the reaction parameters.

The products obtained from the systems **1a**/$H_2N(CH_2)_2OH$ and **1a**/PhN_2H_3 (**3a** and **4a**, respectively) were the Z,Z isomers. **4a** presented a remarkably symmetric crystalline structure with the phenyl rings arranged in a tetrahedral geometry.

The differences in the reaction path and products were rationalized considering the electronic delocalization possibilities of both compounds. This structural difference also explained the considerable smaller equilibrium constant for the monoaddition of Et_2NH to **1b** as compared with the same addition to **1a**.

Supplementary information

A blank CV of the 0.1 M $NaClO_4$ supporting electrolyte solution in DMF and a series of ^{13}C-NMR spectra for the **1a**–*n*-$BuNH_2$ system, including the synthesized **2a** product, and the spectra scanned after the following reaction times: 2 h, 1 week, and 45 days, as described in 'Results and Discussion.'

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