

Synthesis of an α -amino nitrile and a bis α -amino nitrile derivative of thiadiazole: reaction mechanism

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Received 23 May 2007; revised 23 July 2007; accepted 24 July 2007

ABSTRACT: The first nucleophilic addition of an inorganic nucleophile (cyanide) to the activated, rigid, α -diazomethine groups of a 1,2,5-thiadiazole 1,1-dioxide is reported here. An α -amino nitrile and a bis α -amino nitrile derivatives were obtained in good yields (62 and 98%, respectively) and characterized by spectroscopic, analytical, and single crystal X-ray diffraction techniques. The course of the reaction, followed by cyclic voltammetry (CV), showed that cyanide adds to only one of the two C=N double bonds of the thiadiazole, forming an anion from which an *N*-methyl derivative was obtained. Adequate concentrations of cyanide and methyl iodide (MeI) produced directly the bis α -amino nitrile derivative. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: nucleophilic addition; thiadiazole heterocycles; sequential reaction; cyclic voltammetry; X-ray diffraction

INTRODUCTION

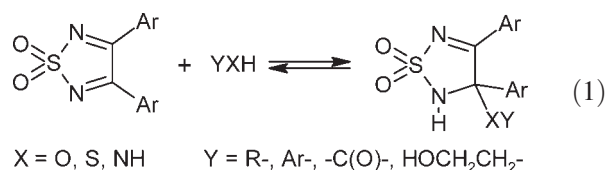
1,2,5-Thiadiazoles, -thiadiazolines, and -thiadiazolidines are broadly applied in the areas of pharmaceutical, agricultural, industrial, and polymer chemistry.¹ In several of these applications, 1,1-dioxide and 1-oxide derivatives are employed.^{2–6}

We have studied many aspects of the chemistry and physical-organic chemistry of 1,1-dioxides^{7–20} and 1-oxides derivatives,^{21,22} particularly structure-reactivity analysis, electrochemical properties, and addition reactions of organic nucleophiles.

However, the possible addition reactions of inorganic nucleophiles have not been explored so far, despite the chemical functionalization and synthetic possibilities that they might offer. This work reports the first study of this kind. We have selected 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide (**1**) as the substrate and the cyanide anion (NC⁻)^{23–25} as the nucleophile, due to the importance of nitriles as organic synthesis intermediates.²⁶

In connection with this work, it is convenient to recall two aspects of our previous reports on nucleophilic addition reaction to thiadiazoles.

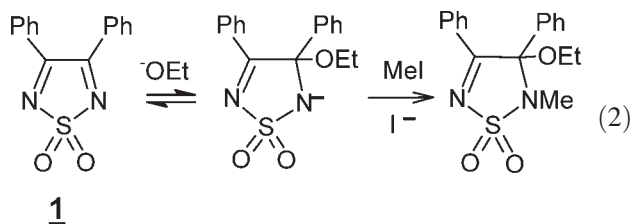
In the first place, we have found that alcohols, thiols, aromatic monoamines, and monocarboxamides in aprotic solvent solution,^{9,10,12,15,19,20} and ethoxide in absolute ethanol solution⁹ add to only one of the two C=N double bonds of **1** and other related thiadiazoles in an equilibrium reaction [Eqn (1)]. This decrease in reactivity after the first addition was also observed in the reaction of **1** with Grignard reagents.²⁷ We have rationalized the difficulty of diaddition reactions, based in the structural details obtained through X-ray diffraction studies and theoretical calculations.¹⁹



The monoaddition products are stable in solution, but non-isolable, reverting to the reactants on solvent evaporation. However, we have found⁹ for the addition reaction of EtO⁻ to **1** that a stable and isolable *N*-methyl

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substituted thiadiazoline can be obtained if methyl iodide (MeI) is incorporated to the reaction before work-up [Eqn (2)].



Secondly, we have also reported that primary aliphatic amines and phenylhydrazine add to both C=N double bonds,¹⁷ but the products are unstable and, losing sulfamide, give α -bis-imines or α -bis-hydrazone, respectively.

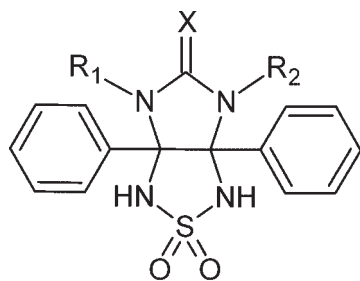
Stable diaddition products are obtained with bifunctional nitrogen nucleophiles such as mono- and symmetrically disubstituted ureas and thioureas, which add to both C=N double bonds of **1** yielding bicyclic compounds (Fig. 1).¹⁶

We report in this work that, depending on the reaction conditions, both monoaddition and diaddition to **1** took place in the case of the CN⁻ nucleophile. The addition reaction products were isolated as a *N*-methyl substituted thiadiazoline (**2**, for monoaddition) or a *N,N'*-dimethyl disubstituted thiadiazolidine (**3**, for diaddition).

The course of the reactions was followed by cyclic voltammetry (CV), used as an electrochemical spectroscopic technique²⁸: the peak potential (E_p) was used to characterize a chemical species (reagent, intermediate, or product) and the current intensity of the peak (I_p) was employed as a concentration measure.

EXPERIMENTAL

Compound **1** was synthesized according to Wright.²⁹ Standard methods were used for purification of MeCN and DMF commercial solvents.^{30–32} Purified solvents were further dried with freshly activated 4A molecular sieves and stored under a dry nitrogen atmosphere in a



X = O, S; R = H, alkyl

Figure 1. Stable products obtained by the addition of mono- and symmetrically disubstituted ureas and thioureas to both C=N double bonds of **1**

glove-box. Their water content (<30 ppm) was measured by Karl–Fischer coulometric titration.

Commercial potassium cyanide (KCN) was dried over P₂O₅ at reduced pressure and room temperature.

¹H and ¹³C NMR spectra were measured with a Bruker 200 MHz instrument and IR spectra with a Shimadzu IR-435 spectrophotometer (KBr disc).

Solution preparation, synthesis reactions, and other manipulations were made in a glove-box under a dry nitrogen atmosphere at room temperature (*ca* 25 °C).

Single crystals of the compounds were obtained from MeCN solutions by slow evaporation of the solvent.

Single crystal X-ray data for **3** were obtained with a KappaCCD diffractometer, using φ and ω scans and graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) in the ϑ range from 3.33 to 25.00°. Compound **2** was measured with an Enraf-Nonius CAD-4 diffractometer, using the $\omega - 2\vartheta$ scan technique and graphite monochromated CuK α radiation ($\lambda = 1.54184 \text{ \AA}$) in the ϑ range from 3.60 to 68.01°.

The structures were solved by direct and Fourier methods and the final molecular model obtained by full-matrix least-squares refinement on F^2 , employing the SHELXS-97 and SHELXL-97 programs. The hydrogen atoms of both compounds were positioned stereochemically and refined with the riding model. The methyl hydrogen atoms locations were optimized during the refinement by treating them as rigid bodies which were allowed to rotate around the corresponding N–C bond.

2,5-Dimethyl-3,4-diphenyl-1,2,5-thiadiazolidine-3,4-dicarbonitrile 1,1-dioxide (**3**)

1 (224.1 mg, 0.83 mmol) and KCN (159 mg, 2.4 mmol) were added to the DMF solvent (10 ml). The mixture was stirred for 1.5 h at r.t. (*ca* 25 °C). The colorless solution gradually developed a yellow–green color. MeI (496.5 mg, 3.5 mmol) was added to the reaction mixture and the solution was left to stand overnight until the color vanished. Evaporation of the solvent at 35 °C and reduced pressure yielded a solid residue which was washed with copious H₂O and dried at reduced pressure at 40 °C (crude: 290.0 mg). The crude product was recrystallized (Cl₂CH₂-*n*-Hex) at r.t. to give 284.4 mg (0.81 mmol) of a chromatographically (TLC) pure white solid **3** in 98% yield; mp 260.0–261.0 °C. An identical procedure, except that MeCN was the solvent employed, produced a lower yield (55%) of the same solid.

IR(KBr): 3050 (vw, C_{Ar}–H), 2995, and 2910 (w, C_{Aliph}–H), 2480 (vw, C≡N), 2310 (vw, C≡N), 1600 (vw, Ph), 1490 (m), 1335 and 1320 (shoulder) (s, SO₂), 1225 (s), 1165 (s, SO₂), 1140 (s), 1110 (s), 1085 (m).

Anal. Calcd for C₁₈H₁₆N₄O₂S: C: 61.35; H: 4.58; N: 15.90; O: 9.08; S: 9.10. Found: C: 60.47; H: 4.46; N: 15.89; S: 9.54.

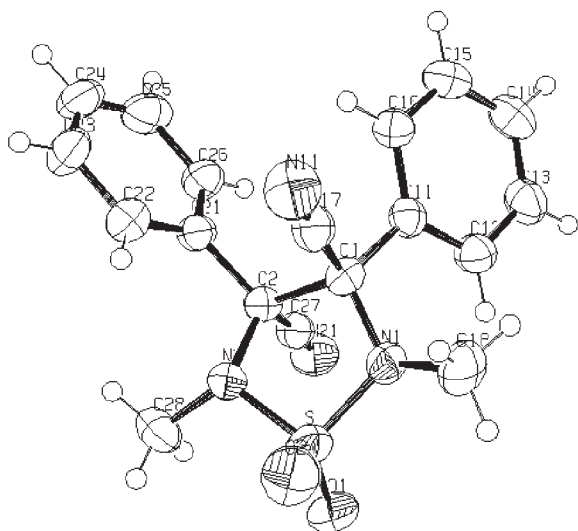


Figure 2. Molecular plot of **3** showing the labeling of the non-H atoms and their displacement ellipsoids at the 50% probability level

^1H NMR (Cl_3CD): δ : 7.60–7.34 (m, 10H, H—C_{Ar}), 2.90 (s, 6H, N—CH₃).

^{13}C NMR (Cl_3CD): δ : 131.7, 129.1, 128.4, 127.1 (C_{Ar}), 112.6 (C≡N), 74.2 (C_{sp}³_{heteroc}), 30.2 (N—CH₃).

$\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$, $M = 352.41$, crystal dimensions $0.20 \times 0.20 \times 0.16$ mm, crystal system, space group: orthorhombic, $P2_12_12_1$, $a = 10.077(1)$ Å, $b = 12.324(1)$ Å, $c = 14.084(1)$ Å, $V = 1749.1(3)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.338$ g cm⁻³, $R1 = 0.0381$ [2591 reflections with $I > 2s(I)$], residual electron density 0.149 – 0.237 eÅ⁻³. An ORTEP³³ diagram of **3** is shown in Fig. 2.

5-Methyl-3,4-diphenyl-1,2,5-thiadiazoline-4-carbonitrile 1,1-dioxide (**2**)

1 (141.3 mg, 0.52 mmol) and KCN (45.5 mg, 0.7 mmol) were added to DMF (50 ml) under agitation and the mixture was stirred for 1.5 h at r.t. A yellow–green color developed after 10 min. The reaction mixture was left to stand overnight. Upon MeI addition (227.0 mg, 1.6 mmol), the green–yellow color decreased very slowly. After 48 h, the solvent was evaporated at 40 °C and reduced pressure from the almost colorless solution. The light-yellow pasty residue obtained was dried at 40 °C and reduced pressure for 5 days, producing a viscous, caramel colored, oil containing a white powder suspension. Extraction with copious CH_2Cl_2 (10×1 ml) left a white solid residue, identified as KI, and a caramel colored solution that was treated with activated charcoal and concentrated at r.t. under reduced pressure until a light opalescence was observed. Upon refrigeration (4 °C), large slightly off-white crystals formed. The filtered crystals were washed with *n*-hexane and dried under reduced pressure at 40 °C. The chromatographically (TLC) pure solid obtained was identified as **2** (99.7 mg, 0.32 mmol, 62%), mp 135.0–135.5 °C.

IR(KBr): 3050 and 3030 (w, doublet, C_{Ar}—H), 2930, 2900, and 2850 (w, C_{Aliph}—H), 2310 (vw, C≡N), 1590 (s), 1540 (s), 1490 (m), 1470 (m), 1450 (s), 1340 and 1320 (shoulder) (s, SO₂), 1165 (s, SO₂).

Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$: C: 61.72; H: 4.21; N: 13.50; O: 10.28; S: 10.30. Found: C: 61.59; H: 4.30; N: 13.46; S: 10.58.

^1H NMR (DMF-*d*₇): δ : 8.04–7.58 (m, 10H, H—C_{Ar}), 2.85 (s, 3H, N—CH₃).

^{13}C NMR (DMF-*d*₇): δ : 171.1 (C_{sp}²_{heteroc}), 136.4, 131.8, 131.2, 131.0, 130.9, 130.3, 127.4, 126.8 (C_{Ar}), 113.6 (C≡N), 72.4 (C_{sp}³_{heteroc}), 26.7 (N—CH₃).

$\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$, $M = 311.35$, crystal dimensions $0.20 \times 0.16 \times 0.16$ mm, crystal system, space group: monoclinic, $P2_1/a$, $a = 11.028(2)$ Å, $b = 11.243(2)$ Å, $c = 12.441(2)$ Å, $\beta = 99.49(2)^\circ$, $V = 1521.4(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.359$ g cm⁻³, $R1 = 0.0394$ [2202 reflections with $I > 2s(I)$], residual electron density 0.269 – 0.291 eÅ⁻³. An ORTEP³³ diagram of **2** is shown in Fig. 3.

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 cm² 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 0.2–0.3 M NaClO₄. The sweep rate (ν) was 0.2 V s⁻¹. A LYP-M2 potentiostat, a three-module LYP sweep generator, and a Houston Omnigraphic 2000 pen recorder were used.

As above mentioned, CV was used as an electrochemical spectroscopic technique to follow the course of the reactions: in a typical experiment, a solution of the reactants at selected initial concentrations and 1/KCN

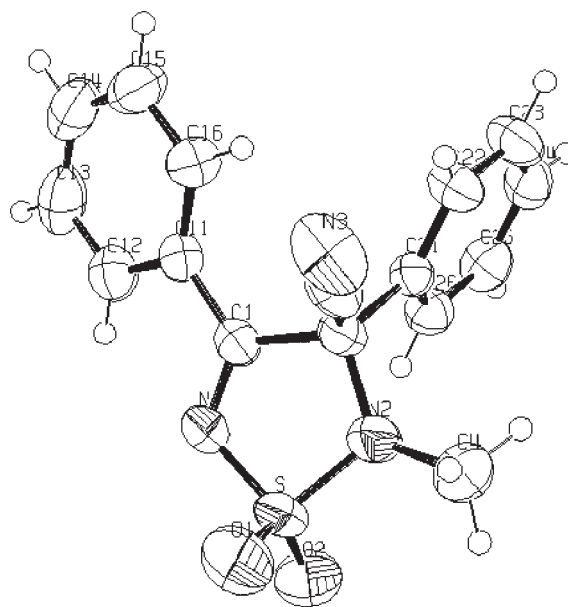


Figure 3. Molecular plot of **2** showing the labeling of the non-H atoms and their displacement ellipsoids at the 50% probability level

molar ratio was prepared and its CVs scanned at convenient reaction times until a time-independent CV was obtained. MeI, in a large stoichiometric excess, was then added to the solution, and new CV scans were run. When no further changes were observed in the CV, the MeI excess was eliminated by dry N₂ bubbling and a final CV was scanned.

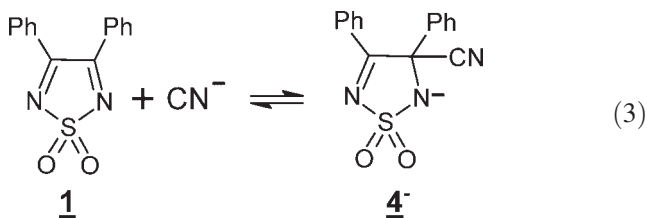
RESULTS AND DISCUSSION

It was found that when an excess of MeI was added to a solution of **1** and KCN in a molar concentration ratio $R = [\text{KCN}]_0/[\mathbf{1}]_0$ ca 3 the **3** thiadiazolidine was obtained, whereas the thiadiazoline **2** was the product if an excess of MeI was added to a solution with R slightly larger than 1 (see Section 'Experimental'). ORTEP diagrams of these reaction products are shown in Figs 2 and 3, respectively.

To obtain information on the course of the reaction, the CV experiments detailed below were performed.

The CV scans of DMF solutions of **1** and KCN in equimolar concentrations ($R = 1$) showed, immediately after their preparation, a gradual decrease to an almost complete disappearance of the two reversibly couples of **1** ($\mathbf{1}/\mathbf{1}^{\cdot-}$ at ca -0.8 V and $\mathbf{1}^{\cdot-}/\mathbf{1}^{2-}$ at ca -1.4 V),¹⁶ along with the appearance and development of a new cathodic peak at ca -2.2 V. A final CV was reached in which a weak signal corresponding to the electroreduction of **1** remained while the current intensity of the peak at -2.2 V reached a maximum constant value (Fig. 4, solid line). Two anodic peaks were also observed, labeled in Fig. 4 as 1a and 2a, their peak potentials correspond to the successive electrooxidation of $\mathbf{1}^{2-}$ to $\mathbf{1}^{\cdot-}$ (peak 1a, Fig. 4) and of $\mathbf{1}^{\cdot-}$ to **1** (peak 2a, Fig. 4).

Experiments described below allowed the assignment of the -2.2 V peak to the anion $\mathbf{4}^-$, formed by the addition of CN⁻ to **1** [Eqn (3)].



The weak CV signal corresponding to the $\mathbf{1}/\mathbf{1}^{\cdot-}$ couple remained after the addition of MeI. The reversibility of the CN⁻ addition reaction [Eqn (3)] and the consumption of CN⁻ through its reaction with MeI, which are further discussed below, account for these observations.

Similar experiments performed with different reactant concentration ratios showed that, for a given initial concentration of **1**, the increase of R up to ca 1.3 caused a proportional peak current intensity increase of the -2.2 V peak, but experiments up to $R = 9$, the highest ratio experimentally measured, left the -2.2 V peak, corre-

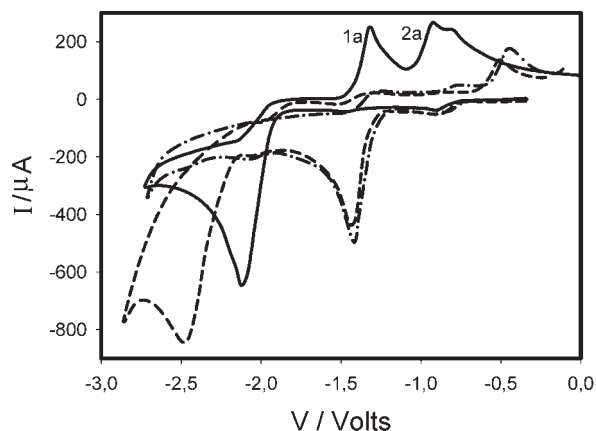


Figure 4. (—) CV of **1** (12.6 mM) and KCN (12.6 mM); (---) after addition of MeI (0.072 M); (-•-) after dry nitrogen bubbling to eliminate MeI excess. DMF solvent, sweep rate: 0.200 V s⁻¹, supporting electrolyte: NaClO₄ (0.25 M)

sponding to the $\mathbf{4}^-$ anionic species, unchanged, and did not produce any other changes in the CVs. Thus, it was concluded that the CN⁻ monoaddition reaction [Eqn (3)] was the only reaction taking place in the **1**/KCN solution. This was further supported by the ¹³C NMR spectrum of the **1**/KCN system, which showed, besides the eight signals of the phenyl C-atoms, one sp² and one sp³ heterocyclic C-atom signals (170.6 and 75.5 ppm, respectively) and one sp C-atom signal (120.4 ppm). These chemical shifts were similar to those of the corresponding C-atoms of the synthesized **2** (see Section 'Experimental'). Since CV peak intensities, in the same experimental conditions, are proportional to concentrations, the current intensity of the **1** peak in the presence of an equimolar amount of KCN, $I_p([\mathbf{1}]_0 = [\text{KCN}]_0)$, in DMF solvent was compared with the current intensity of a DMF solution of **1** at the same concentration, $I_p([\mathbf{1}]_0)$, to obtain a measure of the extent of reaction $R_{\text{ex}} = \{I_p([\mathbf{1}]_0) - I_p([\mathbf{1}]_0 = [\text{KCN}]_0)\}/I_p([\mathbf{1}]_0)$. Figure 5 (circles) shows that R_{ex} increased with an increase in the concentration of reactants. An equilibrium constant for Eqn (3) [$K = (9.3 \pm 1) \times 10^3 \text{ M}^{-1}$] was estimated by a nonlinear fit of the R_{ex} experimental values to the equation $R_{\text{ex}} = \{-(4K[\mathbf{1}]_0 + 1)^{1/2} + 2K[\mathbf{1}]_0 + 1\}/(2K[\mathbf{1}]_0)$ (solid line, Fig. 5).

The initial reactant concentrations and the experimental current intensity of the $\mathbf{4}^-$ CV peak ($I_p\mathbf{4}^-$) are listed in Table 1. The equilibrium concentration of $\mathbf{4}^-$ ($[\mathbf{4}^-]$), calculated using the estimated K and the initial concentrations of the reactants, is also included. A least-squares linear regression gave $I_p\mathbf{4}^-/\mu\text{A} = 60 \mu\text{A} + (4.0 \pm 2) \times 10^4 \mu\text{A M}^{-1} \times [\mathbf{4}^-]$ ($r = 0.96$).

The functional relation between $\mathbf{4}^-$ concentration and the current intensity of its electroreduction peak ($I_p\mathbf{4}^-$) was indicated by the fact that $\mathbf{1}^{2-}$ was its electroreduction product (Fig. 4, peaks 1a and 2a). Thus, the first charge transfer to $\mathbf{4}^-$ should produce the corresponding radical dianion $\mathbf{4}^{\cdot 2-}$, which decomposes rapidly to $\mathbf{1}^{\cdot-}$ and CN⁻.

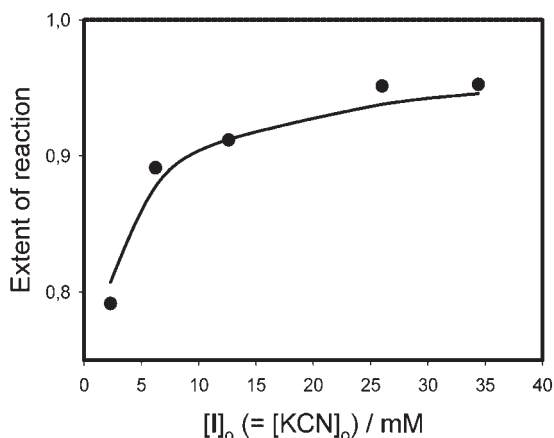
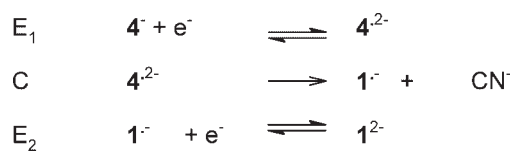


Figure 5. Extent of reaction [Rex, Eqn (3)] as a function of reactant concentration at equal initial concentrations of **1** and KCN. The extent of reaction was measured voltametrically as $Rex = [I_p(\mathbf{1})_o - I_p([\mathbf{1}]_o = [\text{KCN}]_o)] / I_p(\mathbf{1})_o$, where, for a given concentration of **1**, $I_p(\mathbf{1})_o$ is the current intensity of the first CV peak of **1**, and $I_p([\mathbf{1}]_o = [\text{KCN}]_o)$ is the current intensity of the same peak in the presence of KCN. Circles indicate experimental measurements. The solid line is a nonlinear regression adjustment of the points to the equation $Rex = [- (4K[\mathbf{1}]_o + 1)^{1/2} + 2K[\mathbf{1}]_o + 1] / (2K[\mathbf{1}]_o)$, which gave $K = (9.3 \pm 1) \times 10^3 \text{ M}^{-1}$.

Since the electroreduction potential of $\mathbf{1}^{\cdot -}$ is ca -1.4 V , it would be immediately electroreduced at -2.2 V to $\mathbf{1}^{2-}$. The electrode process would be an E_1CE_2 process (Scheme 1).

The dependence of the CV peak current intensity with the experimental parameters for an E_1CE_2 process, with $E_2 \gg E_1$, and assuming that the chemical step C is very fast, is very well known:³⁴ $I_p\mathbf{4}^- = (n_1 + n_2)FAD^{1/2} (n_1F/RT)^{1/2} \nu^{1/2} [\mathbf{4}^-] \pi^{1/2} \chi(at)$.

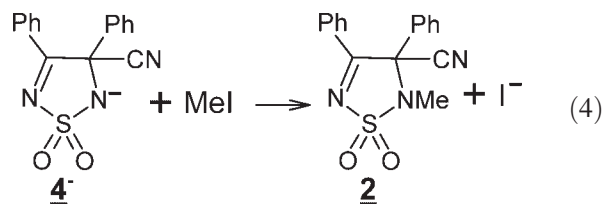
If these conditions are met, the peak value for the function $\pi^{1/2} \chi(at)$,³⁴ is 0.487. These, together with our experimental values (sweep rate, $\nu = 0.2 \text{ V s}^{-1}$, working



Scheme 1.

electrode area, $A = 0.071 \text{ cm}^2$, diffusion coefficient, D of the substrate $= 1 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, give $I_p\mathbf{4}^- = 5.9 \times 10^4 \times [\mathbf{4}^-] \mu\text{A}$. This was considered an acceptable agreement, given the approximate nature of the calculations involved.

When an excess of MeI was added to an equimolar or nearly equimolar solution ($R \cong 1$) of **1** and KCN that had undergone the changes described above, the CV scanned after the MeI addition showed a gradual intensity decrease of the cathodic peak at -2.2 V (although somewhat obscured by the MeI peak at -2.5 V), along with the development of a new cathodic peak at ca -1.4 V (Fig. 4, broken line). When the MeI excess was eliminated from the solution by dry N_2 bubbling, only the peak at ca -1.4 V (Fig. 4, dash-dot-dash line) remained. The peak at -1.4 V was assigned to the electroreduction of **2**, formed in the reaction of Eqn (4), by comparison with an authentic sample (a CV scan of a DMF solution of **2** is shown in Fig. 6, solid line).



The MeI incorporated to the **1**/KCN reaction mixture also reacted with CN^- to give MeCN and iodide ion (see

Table 1. Experimental initial concentrations of reactants and measured peak current for the $\mathbf{4}^-$ peak at -2.2 V

$[\mathbf{1}]_o$ (mM)	$[\text{KCN}]_o$ (mM)	I_p (μA)	$[\mathbf{4}^-]$ calc. (mM)	I_p (calc.) (μA)
2.13	4.30	100	2.03	141
2.31	2.33	108	1.87	135
7.74	3.68	138	1.71	128
8.16	23.0	272	8.10	384
12.6	6.44	275	3.24	189
7.85	20.0	300	7.78	371
6.3	6.30	305	5.53	281
7.78	28.0	335	7.74	370
7.70	28.0	345	7.66	366
7.44	25.0	354	7.40	356
7.45	67.6	382	7.44	357
12.6	25.5	500	12.5	560
12.4	24.0	560	12.3	552
12.6	12.6	609	11.5	520
12.6	16.7	629	12.3	552
12.6	56.5	660	12.6	563
25.0	25.0	950	23.4	997
34.5	34.5	1140	32.6	1365

The calculated $\mathbf{4}^-$ concentration, based on $K_{eq} = 9.3 \times 10^3 \text{ M}^{-1}$ for the reaction of Eqn (3), and the calculated peak currents, based on a linear least-squares regression (see text) are also listed.

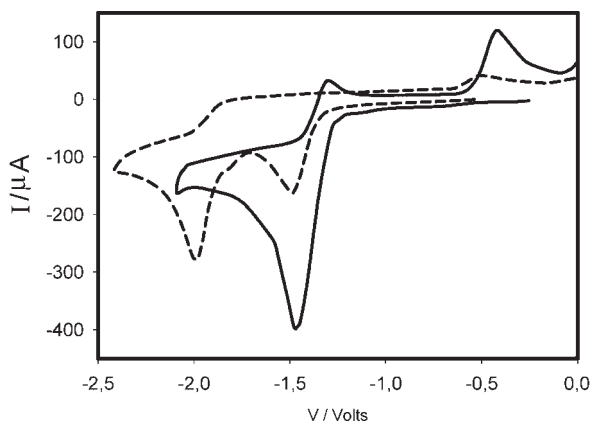


Figure 6. (—) CV of **2** (13.2 mM); (---) after addition of KCN (8.22 mM). DMF solvent, sweep rate: 0.200 V s^{-1} , supporting electrolyte: NaClO_4 (0.25 M)

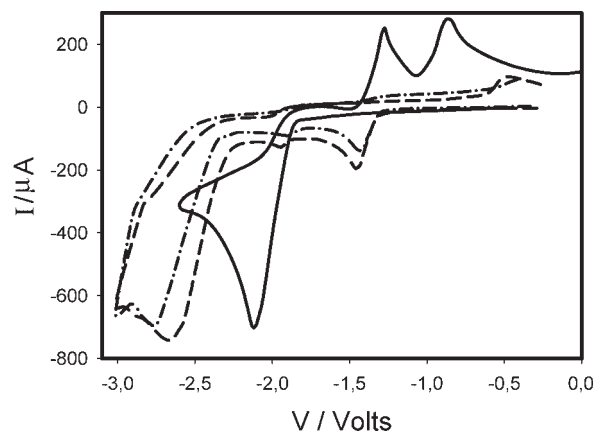
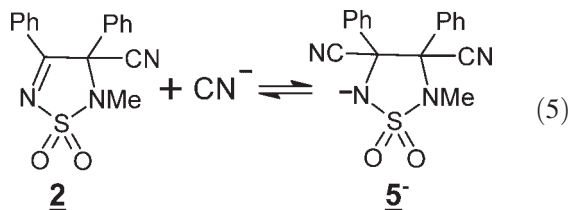


Figure 7. (—) CV of **1** (12.6 mM) and KCN (56.6 mM); (---) after addition of MeI (0.13 M); (-•-) after dry nitrogen bubbling to eliminate MeI excess. DMF solvent, sweep rate: 0.200 V s^{-1} , supporting electrolyte: NaClO_4 (0.25 M)

the synthesis of **2**, Section 'Experimental'), it must be concluded that, in our reaction conditions, the N-methylation of **4**⁻ [Eqn (4)] was favored over the loss of CN^- [back reaction of Eqn (3)] followed by the reaction of CN^- with MeI. However the balance left some unreacted substrate **1**, as observed (Fig. 4, dash-dot-dash line). The ideal experimental conditions for the highest possible yield of **2** were not further investigated.

It was found that addition of CN^- to the remaining C=N double bond of **2** also took place. In a CV experiment in which KCN was added to a DMF solution of **2** to a $[\text{KCN}]_0/[\mathbf{2}]_0$ molar ratio of 0.62 (initial concentrations: 13.2 mM **2**; 8.22 mM KCN), it was observed that the CV peak of **2** (Fig. 6, solid line) decreased with time while a new cathodic peak at -1.99 V developed. When all changes ceased (Fig. 6, broken line), the CV showed that the current intensity of the peak of **2** had decreased to *ca* 37% of its original current intensity of $378 \mu\text{A}$, while the current intensity of the new peak at -1.99 V was $200 \mu\text{A}$, that is, 53% of the original intensity of the **2** peak.

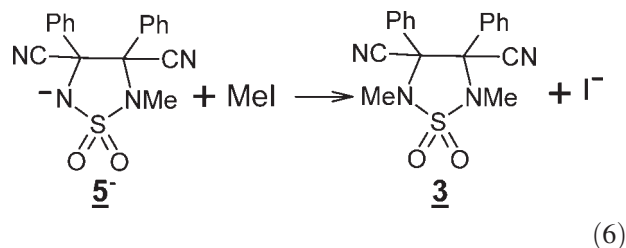
This result indicates that practically all CN^- has reacted to give a new species that is reduced at -1.99 V . It seemed reasonable to assign the peak at -1.99 V to a thiadiazolidine anion produced by the CN^- addition to the remaining C=N double bond of **2** anion [**5**⁻, Eqn (5)].



Thus, the neutral molecule **2** added CN^- , but the **4**⁻ anion did not. This is of course reasonable, because the effect of electron-withdrawing properties of the $>\text{SO}_2$ group on the remaining sp^2 heterocyclic C-atom must be

much weaker for the anion. PM3 calculations gave fractional electron charges on the heterocyclic sp^2 C-atom of 0.15 for **2** and -0.16 for **4**⁻.

The assignment of the -1.99 V CV peak to **5**⁻ was further supported when, upon addition of MeI, the peak at -1.99 V disappeared and was replaced by a peak of similar current intensity at -2.7 V (not shown in Fig. 6). As it is discussed immediately below, the peak at -2.7 V corresponds to the thiadiazolidine **3** [Eqn (6)].



Thiadiazolidine **3** was also observed in CV experiments performed at a larger $[\text{KCN}]_0/[\mathbf{1}]_0$ relation (e.g., Fig. 7; $R=4.5$). As above mentioned, the initial changes were almost identical to those observed for $R \text{ ca } 1$ (Fig. 7, solid line). After an excess of MeI was added, the resulting CV peak of **2** at *ca* -1.4 V was much smaller than for $R=1$, and a large, broad peak was observed at *ca* -2.7 V (Fig. 7, broken line). Upon elimination of the MeI excess it was observed (Fig. 7, dash-dot-dash line) that the broad peak was a superimposition of the MeI peak at -2.5 V and a new cathodic peak at *ca* -2.7 V . The peak at -2.7 V was assigned to the electroreduction of **3** by comparison with an authentic sample.

CONCLUSIONS

The CN^- nucleophile adds to one or to both azomethine groups of **1**. The corresponding thiadiazoline or

thiadiazolidine are obtained in good yields and can be isolated by standard procedures. This contrasts with previously studied nucleophilic addition reaction of monodentate nucleophiles which produced only mono-addition to give thiadiazolines, most of which were only stable in solution, reverting to the reactants on work-up, or unstable diaddition thiadiazolidines which decomposed losing the sulfamide moiety.¹⁸

To the best of our knowledge, only two methods have been reported for the formation of a carbon-carbon bond between the heterocyclic C-atoms of **1** and a substituent, the first uses Grignard reagents²⁷ and the second employs a very strong acid catalyst (AlCl₃).¹⁵ The synthesis reported here takes place under mild conditions and can be easily adjusted to produce mononitrile or dinitrile derivatives, which are well known for their usefulness in synthetic routes.

The reactions steps were unambiguously clarified by the use of CV. This demonstrates once again the merits of this electrochemical technique for the elucidation of organic reactions mechanisms and the detection of intermediates.

In particular, it was shown that mono and diaddition did not take place consecutively on the same substrate. Instead, it was necessary to N-methylate the monoaddition nitrile before a second CN⁻ anion could be added.

Acknowledgements

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.), and the Universidad Nacional de La Plata (UNLP), Facultad de Ciencias Exactas, Departamento de Química and Facultad de Ingeniería, Departamento de Ingeniería Química. M. V. M., J. A. C., and O. E. P. are researchers of CONICET and UNLP, E. J. V. is researcher of CIC Pcia. Bs. As. and UNLP.

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