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The CSIC Reaction on Substrates Derived From Aldehydes

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Abstract—The Carbanion-mediated Sulfonate (Sulfonamide) Intramolecular Cyclization reaction (CSIC reaction) on conveniently functionalized cyanoalkylsulfonates and cyanoalkylsulfonamides derived from aldehydes is possible and gives the new heterocyclic ring systems 5-alkyl-4-amino-5*H*-1,2-oxathiole 2,2-dioxide and 3-alkyl-5*H*-4-amino-5-cyano-5*H*-2,3-dihydroisothiazole 1,1-dioxide in good yield.

Introduction

The CSIC reaction[1,2] is an intramolecular cyclization brought about by the treatment of either cyanohydrin or aminonitrile alkylsulfonates with non-nucleophilic bases such as DBU or NaH.[2–8] This reaction is related to the aldol, Dieckmann and Thorpe–Zeigler reactions[9] but is novel in that a cyanide group acts as the carbonyl component and the active methylene species comes from the α-carbon attached to the SO_2 group of the alkylsulfonate moiety[10] (Scheme 1). This reaction was first observed as an anomalous process occurring in sugar based cyanomesylates[8] where the desired reaction would have been a β-elimination to leave a cyano group attached to a double bond. Instead of the desired reaction, the novel 3-(5-spiro-4-amino-1,2-oxathiole 2,2-dioxide) (or 4-aminospiro-γ-sultone) ring was generated. This unusual synthetic event was later exploited for the formation of the 4-amino-γ-sultone found in the TSAO nucleosides that have been shown to be interesting inhibitors of the multiplication of the AIDS virus HIV-1.[11] Apart from sugar based derivatives, these 4-aminospirosultones were also made from cyclic ketones such as adamantane[3] and quinuclidine.[4]

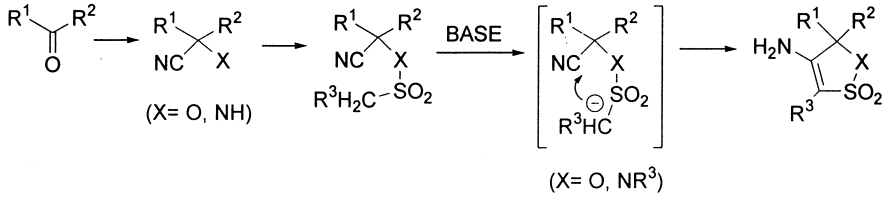
In recent years we have shown that alkylsulfonates, other than mesylates, may also act as the active methylene species in this reaction, extending the utility of the CSIC reaction, since new derivatives containing substitutions at the carbon adjacent to the SO_2 group are thus available.[5,6] We first demonstrated that the previously unknown 4-amino-5*H*-2,3-dihydroisothiazole 1,1-dioxides can be made using the CSIC reaction involving suitably substituted alkylsulfonamides derived from α-aminonitriles accessible from acetone via the Strecker reaction.[5] Similarly, straight chain ketones can be used as the starting materials[6,7] for the production of 4-amino-5*H*-1,2-oxathiole 2,2-dioxides.

Until now only relatively simple ketones as sources of the cyanohydrin and aminonitrile intermediates required for the study of this cyclization have been looked into. In this paper we will report on our efforts to understand the scope and limitations of this process by using derivatives of aldehydes as the starting materials.

Results and Discussion

Chemistry

We first wished to establish whether the CSIC reaction



Scheme 1. The CSIC reaction.

Keywords: cyanoalkylsulfonates; cyanoalkylsulfonamides; non-nucleophilic bases.
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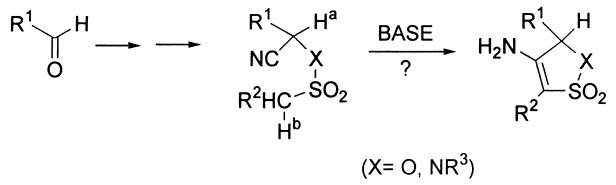


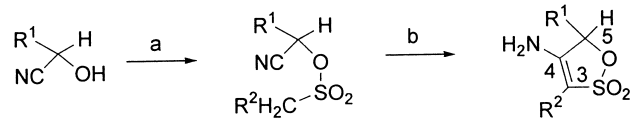
Scheme 2. Presumed CSIC reaction on suitable aldehyde derivatives.

could be carried out on substrates derived from aldehydes, i.e. is a quaternary carbon adjacent to the nitrile group necessary for the successful outcome of the cyclization? One complication that we envisaged was the possibility that the proton H^a (the aldehydic proton) may be more acidic than H^b of the alkylsulfonate. Should this be the case, then basic treatment of these substrates would favor the removal of H^a making the CSIC reaction less likely than other processes (Scheme 2). Literature sources had already shown that aromatic sulfonates of mandelonitrile (R^1=Ph) indeed underwent elimination reactions.[12] Effenberger had demonstrated that the mesylates of cyanohydrins may undergo S_N2 reactions with methylsulfonyl acting as a leaving group.[13]

The alkylsulfonyloxynitrile derivatives required for this study were obtained either from commercial lactonitrile (**2a** and **2b** via **1a**) or propanal (**2c**–**e** via **1b**) in good yields (Scheme 3) (see Experimental). When these compounds were treated with sodium hydride in acetonitrile they cyclized rapidly (5 min–1.5 h) to yield the products (**3a**–**3e**). On the other hand the *O*-methylsulfonate of mandelonitrile (**2f**) did not undergo the CSIC reaction in line with previous reports.[12] The ^{1}H NMR spectra of compounds **3a**–**3e** are characterized by the presence of a one proton multiplet lying within the range 5.00–5.20 ppm due to the proton H-5, the proton derived from the aldehyde, and a two proton exchangeable signal (6.30–6.80 ppm) that indicates the presence of the NH_2 group. The ^{13}C NMR signal for C-5 was observed within the narrow range of 77.4–83.6 ppm, whereas the C-3 signal varied depending upon the group attached to this position (84–85 ppm when R^2=H, 91–92 ppm when R^2=Me and 128 ppm when R^2=Ph).

Clearly the CSIC reaction is favored over elimination in aldehyde derived cyanohydrin alkylsulfonates as long as the aldehyde used was aliphatic and not aromatic. The reason for this would be that the electron withdrawing effects caused by the presence of the phenyl ring, nitrile and the oxygen adjacent to H^a in **2f** favor its removal in preference to the H^b proton of the mesylate. Compounds **3a**–**3e** represent the first published examples of 4-amino-3,5-dialkyl-5*H*-1,2-oxathiole 2,2-dioxides.

In the light of these interesting results we were encouraged to attempt the synthesis of the 4-amino-2,3,5-trialkyl-5*H*-2,3-dihydroisothiazole 1,1-dioxides that would be available from aminonitriles derived from aldehydes. The only difference between these compounds and **3** would be the presence of an alkylated nitrogen atom instead of the ring oxygen. Based upon the above results we expected that the CSIC reaction on the nitrogen bearing substrates should proceed readily. From our previous experience with ketone derived aminonitrilesulfonamides we knew that the central nitrogen atom would have to be fully substituted in order for the CSIC reaction to proceed,[6] otherwise the amino nitrogen would be removed to give insoluble sodium salts of the alkylsulfonamidonitriles. Thus, we decided to limit our studies initially to *N*-methylated or *N*-benzylated intermediates. The methanesulfonyl, ethanesulfonyl and α-phenylmethyl sulfonyl groups were chosen to serve as the active methylene containing parts of the molecule with different levels of activation (Ph>H>Me). In order to examine if the aldehydic proton (H^a) acidity would vary with the degree of steric crowding on the adjacent carbon (i.e. R^1) we chose to make derivatives of formaldehyde (R^1=H), propanal (R^1=Et) and 2-methylpropanal (R^1=*i*-Pr). Two approaches for the synthesis of these compounds (**5a**–**5h**) were adopted, the first involved performing the Strecker synthesis of primary aminonitriles between aldehydes and ammonium chloride and then benzylating their alkylsulfonamide analogues **5a**, **5c** and **5e** to make compounds **5b**, **5d** and **5f**, respectively (Scheme 4). The *N*-benzyl derivatives were made in this way since *N*-benzyl-aminonitriles were known to decompose during the reaction with methanesulfonyl chloride in the presence of triethylamine. Alternatively methylamine hydrochloride was used

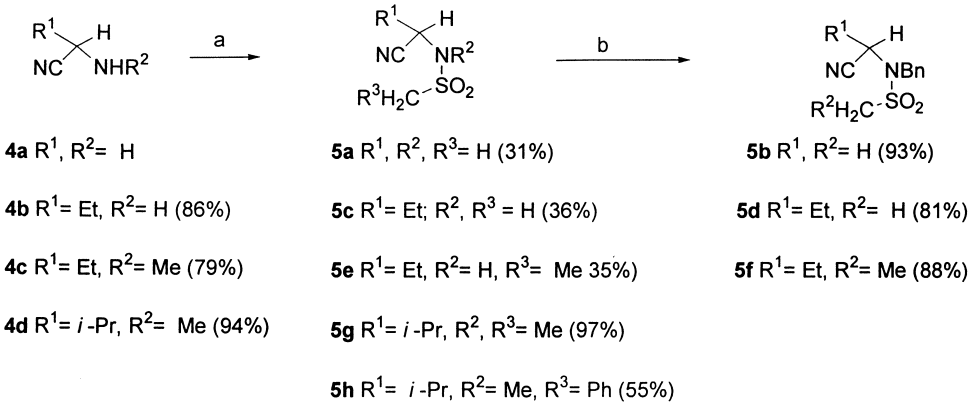


1a R^1= Me
1b R^1= Et
1c R^1= Ph

2a R^1= Me, R^2= H (91%)
2b R^1, R^2= Me (88%)
2c R^1= Et, R^2= H (81%)
2d R^1= Et, R^2= Me (71%)
2e R^1= Et, R^2= Ph (45%)
2f R^1= Ph, R^2= H (83%)

3a R^1= Me, R^2= H (20%)
3b R^1, R^2= Me (58%)
3c R^1= Et, R^2= H (50%)
3d R^1= Et, R^2= Me (84%)
3e R^1= Et, R^2= Ph (91%)

Scheme 3. Synthesis of 4-amino-5*H*-1,2-oxathiole 2,2-dioxides from aldehydes via CSIC reaction. Reagents: (a) $R^2CH_2SO_2Cl$, Et_3N, CH_2Cl_2, 0°C; (b) NaH, CH_3CN, room temperature.



Scheme 4. Synthesis of intermediates **5b**, **5d** and **5f** from formaldehyde and propanal. Reagents: (a) $R^3CH_2SO_2Cl$, Et_3N, CH_2Cl_2, 0°C; (b) BnBr, K_2CO_3, CH_3CN, reflux.

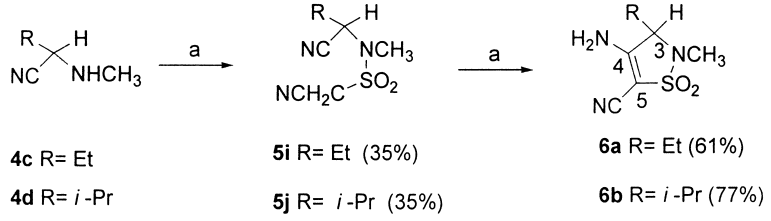
and the *N*-methylaminonitriles **4c**–**d** generated were subsequently reacted with the appropriate alkylsulfonyl chloride (see Experimental).

When compounds **5a**–**5h** were subjected to the standard CSIC reaction conditions (1 equiv. of NaH in acetonitrile at room temperature) no reaction took place even when the conditions were forced (addition of more base or heating to reflux). Upon work-up, addition of water and extraction with CH_2Cl_2 we isolated predominantly the starting material, the slight losses in mass balance could be explained by hydrolytic loss of the alkylsulfonate group in a small proportion of the material (losses generally 5–10%). These results suggest that the aldehydic proton in these alkylsulfonamides must be removed in preference to H^b (Scheme 2). In cyanohydrins, this would lead to the loss of the alkylsulfonate moiety. The possible elimination/addition products similar to those described by Loudon and Wellings in the case of cyanohydrin tosylates[12] were not isolated, suggesting that the carbanion formed upon the removal of H^a may be stabilized electronically, probably by the formation of an iminium ion.

The complete lack of reactivity of these compounds was somewhat surprising especially since in **5h**, the methylene lies between the SO_2 and Ph groups and should be reasonably activated. We decided therefore to synthesize compounds **5i** and **5j** in which the methylene would be sandwiched between a SO_2 and a nitrile. In order to do this it was necessary to make cyanomethylenesulfonyl chloride that is available from chloroacetonitrile in two steps.[14] This reagent is a strong lacrymator and is rather unstable at room temperature, decomposing violently with water and more slowly but with the formation of tars in the presence of trialkylamine bases. Due to its instability we made this product in small batches for immediate use. The cyanomethylene sulfonamide containing analogues **5i** and **5j** were obtained in 35% yield, from **4c** and **4d**, respectively, when pyridine was used as the acid sink, the former product being impossible to obtain in a pure state (Scheme 5). Small amounts of tar were produced during this reaction although much less than when triethylamine was used as the base. The treatment of these sulfonamides with 0.5 equiv. DBU in acetonitrile gave the cyclized compounds **6a** and **6b** in good yields (61 and 77%, respectively) (Scheme 5), the impurity in **5i** was later confirmed to be **6a** that formed spontaneously even during chromatography. The ^1H NMR analysis of these compounds showed the similarities to the related oxygen containing heterocycles **3a**–**e** with H-3 signals for **6a** and **6b** at 4.04–4.12 ppm (cf. 5.0–5.2 ppm in compounds **3** for H-5, the difference in shift being due to the different ring heteroatom). The NH_2 group signal appears at 7.5–7.62 ppm rather than the 6.3–6.8 ppm range observed for **3a**–**3e**.

Theoretical calculations

Assuming the mechanism for the CSIC reaction (Scheme 1), two main reasons can be invoked to explain the reactivity differences between O and N derivatives (compounds **2** and **5)**: (i) a much higher activation energy for **5**; and (ii) the relative acidity of the involved protons (H^a and H^b). The experimental results obtained in the previous section with compounds **2** and **5** have been studied by means of MO semiempirical calculations using the MOPAC program[15] under the AM1 Hamiltonian[16] (see Experimental for details). Computed $\Delta H^{\neq}$ does not seem to have influence over the reactivity (Table 1). Consequently, the relative



Scheme 5. The CSIC reaction applied to α-(cyanomethylene) sulfonamido nitriles derived from propanal and 2-methylpropanal. Reagents: (a) $CNCH_2SO_2Cl$, Et_3N, CH_2Cl_2, 0°C; (b) DBU, CH_3CN, room temperature.

Table 1. Heat of formation (kcal/mol) for **2H**, **5H**, and for their transition states in the CSIC reaction, as well as the activation energy (kcal/mol) as obtained from MOPAC calculations

Compound	Heat of formation (kcal/mol)			Activation energy (kcal/mol)
	Anion over	Starting anion	Transition state	
2H	H^a	−111.5		
	H^b	−128.8	−101.3	27.5
5H	H^a	−58.7		
	H^b	−70.5	−45.4	25.1
	HN	−72.7		

acidity of hydrogens should then have larger influence. In general, the oxygen containing compounds, **2H**, are computed to lose H^b more easily than H^a, favoring the CSIC reaction. In contrast, the nitrogen containing compounds, **5H**, prefer to be deprotonated at the N atom rather than at the C atoms; CSIC reactions are thus impossible.

Only compound **2f** has not produced the CSIC reaction. Computations indicate that, in this case, H^a is less acidic than H^b (ΔH_f for the anions are −90.8 and −94.7 kcal/mol, respectively) indicating the possibility of cyclization, in clear disagreement with experiments, although the preference has now decreased if compared with **2H** (about 4 kcal/mol for **2f** in comparison to around 17 kcal/mol for **2H**). Care has to be taken when computing molecules containing sulfur with semiempirical MO methods.[17] Taking compounds **2f** and **2H** as models, the extra stability in the computation of the α S anion ΔH_f in our studied system should be larger than 4 and smaller than 17 kcal/mol (i.e. around 10 kcal/mol).

None of the NH products (**5a**, **5c** and **5e**) produce the CSIC reaction. The acidity of the different possible anions indicate the most favorable anion is that located at the N atom (Table 1). When the NH group is transformed into the NMe group, as in **5g** and **5h**, the AM1 computations indicate the deprotonation over H^b to be 13.3 kcal/mol more stable than deprotonation over H^a (ΔH_f are −65.3, and −52.0 kcal/mol, respectively); CSIC reaction is thus likely to be possible even if the 10 kcal/mol of extra stabilization is considered. Compounds **5i** and **5j** produce the corresponding cyclic products. Computed ΔH_f for the anions of a model compound (**5H** but where one of the methyl hydrogens was replaced by a cyano group) not surprisingly indicate that deprotonation of H^a is much less favored than the deprotonation of H^b (−25.2, and −54.7 kcal/mol, respectively), in perfect agreement with experiments. Substrates **5b**, **5d** and **5f** have one benzyl group on the N atom. The anion over the benzylic methylene is computed to be only 8.2 kcal/mol less stable than the anion over H^b; the consideration of the ca. 10 kcal/mol of error may change the relative stability order, and consequently the reaction should not proceed smoothly, in agreement with experiments.

Conclusions

The activation energy for the CSIC reaction carried out on aldehyde derivatives does not substantially differ from that for aminonitrile derivatives (about 25–27 kcal/mol computed, not determined). The relative stability of involved anions seems to be the main reason for the experimental achievement of the CSIC reaction as indicated by our semiempirical MO computations.

Experimental

Computational details

All computations, unless otherwise noted, have been performed on the simplest possible substrate to reduce computational expenses (i.e. all R groups were replaced by H) here after called **2H** and **5H**, respectively. The parent substrate for the CSIC reaction contains two rotatable dihedral angles ($NC–CH_2–X–SO_2$, and $CH_2–X–SO_2–CH_3$). All possible rotamers have been computed and their stabilities were evaluated in each case (X=O and NR). The heat of formation of the cyclized product from the starting product, **2H** or **5H**, was obtained by application of the Boltzmann distribution over all the conformers obtained by systematic rotation of the two above-mentioned bonds. The corresponding transition states for cyclization were located by elongating the corresponding bond on the imine anion obtained after the internal nucleophilic attack of the anion on the nitrile group.

General methods

Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric–acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry organic solutions during work-ups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, Merck) and hexane–ethyl acetate mixtures as eluent unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-200S spectrometer, using tetramethylsilane as internal standard. Compounds **1a**, **1c** and **4a** are commercial and were used as received.

2-Hydroxybutanenitrile (1b).[19] A solution of propanal (3.0 mL, 41.5 mmol) in Et_2O (50 mL) was stirred rapidly with a solution of KCN (2.98 g, 45.7 mmol) and $NaHCO_3$ (7.56 g, 90 mmol) in H_2O (30 mL) at room temperature for 18 h. The aqueous layer was extracted with diethyl ether (3×30 mL) and the combined, dried (Na_2SO_4) ether layers

were used directly for the synthesis of the alkylsulphonates **2c**, **2d** and **2e**.

2-[(Methylsulfonyl)oxy]propanenitrile (2a).[20] To a solution of lactonitrile (**1a**) (3.0 mL, 41.8 mmol) and Et_3N (10.6 mL, 83.6 mmol) in CH_2Cl_2 (75 mL) at 0°C, methanesulfonyl chloride (3.87 mL, 50.1 mmol) was added dropwise. The reaction was stirred at this temperature for 30 min, the solution was washed with water (1×40 mL and then 2×20 mL), the organic solvent was dried (Na_2SO_4) and evaporated. Column chromatography (2:1–1:1, hexane–ethyl acetate) yielded **2a** as a pale yellow oil (5.68 g, 91%) that solidified upon freezing: mp 43–44°C; IR (KBr) ν 1136, 1185 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.75 (d, J=6.5 Hz, 3 H, H-3), 3.13 (s, 3 H, $MeSO_2$), 5.30 (q, J=6.5 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8 (C-3), 38.8 (CH_3SO_2), 62.5 (C-2), 116.2 (CN). Anal. Calcd $C_4H_7NO_3S$: C, 32.21; H, 4.73; N, 9.39; S, 21.49. Found: C, 32.11; H, 4.55; N, 9.10; S, 21.67.

2-[(Ethylsulfonyl)oxy]propanenitrile (2b). To a solution of lactonitrile (**1a**) (1.5 mL, 20.9 mmol) and Et_3N (5.30 mL, 41.8 mmol) in CH_2Cl_2 (30 mL) at 0°C, ethanesulfonyl chloride (2.27 mL, 24.0 mmol) was added dropwise. The reaction was stirred at this temperature for 30 min and then for 3 h at room temperature. The solution was washed with water (3×20 mL), the organic solvent was dried (Na_2SO_4) and evaporated. Column chromatography (3:1, hexane–ethyl acetate) yielded **2b** (3.01 g, 88%) as a pale yellow oil that solidified upon freezing: mp 38–40°C; IR (film) ν 1365, 1175 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J=7.5 Hz, 3 H, CH_3CH_2), 1.72 (d, J=6.5 Hz, 3 H, H-3), 3.25 (q, J=7.5 Hz, 2 H, CH_3CH_2), 5.24 (q, J=6.5 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.8 (CH_3CH_2), 20.0 (C-3), 46.3 (CH_3CH_2), 62.1 (C-2), 116.3 (CN). Anal. Calcd $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; S, 19.65. Found: C, 36.72; H, 5.62; N, 8.34; S, 19.25.

2-[(Methylsulfonyl)oxy]butanenitrile (2c). Crude **1b** (1.15 g, 13.5 mmol, theor.) was dissolved in CH_2Cl_2 (20 mL) containing Et_3N (5.1 mL, 40.5 mmol), the mixture was cooled to 0°C and methanesulfonyl chloride (1.57 mL, 20.3 mmol) was added dropwise. The reaction was stirred for 1 h, was filtered over Celite, the solvent was evaporated and the residue was purified by flash chromatography (3:1, hexane–ethyl acetate) to give **2c** (1.78 g, 81%) as a yellow oil: IR (film) ν 2320 (CN), 1370, 1180 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, J=7.4 Hz, 3 H, H-4), 1.97–2.00 (m, 2 H, H-3), 3.11 (s, 3 H, CH_3SO_2), 5.08 (t, J=6.3 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.6 (C-4), 27.0 (C-3), 38.9 (CH_3SO_2), 67.4 (C-2), 115.5 (CN). Anal. Calcd $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; S 19.65. Found: C, 36.66; H, 5.43; N, 8.39; S 19.33.

2-[(Ethylsulfonyl)oxy]butanenitrile (2d). To a solution of crude **1b** (1.31 g, 15.39 mmol, theor.) and Et_3N (5.85 mL, 46.2 mmol) in CH_2Cl_2 (30 mL) at 0°C, ethanesulfonyl chloride (2.18 mL, 23.1 mmol) was added. The reaction was stirred at room temperature for 4 h, was filtered over Celite and was evaporated to give a residue that was purified by flash chromatography (3:1, hexane–ethyl acetate) to yield **2d** (1.93 g, 71%) as a colorless oil: IR (film) ν 1370, 1185 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (t, J=7.3 Hz, 3 H, $CH_3CH_2SO_2$), 1.50 (t, J=7.5 Hz, 3 H, H-4), 2.03–2.06 (m, 2 H, H-3), 3.28 (q, J=6.5 Hz, 2 H, $CH_3CH_2SO_2$), 5.16 (t, J=6.6 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.9 (C-4), 8.5 ($CH_3CH_2SO_2$), 27.0 (C-3), 46.3 ($CH_3CH_2SO_2$), 67.1 (C-2), 115.6 (CN). Anal. Calcd $C_6H_{11}NO_3S$: C, 40.67; H, 6.26; N, 7.90; S, 18.09. Found: C, 40.37; H, 6.18; N, 7.68; S, 18.12.

2-(Benzenemethylsulfonyl)oxy]butyronitrile (2e). To a solution of crude **1b** (0.38 g, 4.45 mmol, theor.) and Et_3N (1.68 mL, 13.3 mmol) in dichloromethane (20 mL) was added solid α-toluenesulfonyl chloride (1.25 g, 6.6 mmol). The solution was stirred at room temperature for 5 h, hexane (10 mL) was added and the mixture was filtered over Celite. The residue obtained upon evaporation of the solvent was purified by flash chromatography (1:1, hexane–dichloromethane—100% CH_2Cl_2) to give **2e** (0.32 g, 45%) as a colorless syrup that solidified upon standing: mp 35–36°C; IR (film) ν 1370, 1175 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, J=7.5 Hz, 3 H, H-4), 1.95–1.99 (m, 2 H, H-3), 4.51 (s, 2 H, $PhCH_2$), 4.98 (t, J=6.4 Hz, 1 H, H-2), 7.45 (s, 5 H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.5 (C-4), 27.2 (C-3), 58.0 ($PhCH_2$), 68.2 (C-2), 115.4 (CN), 126.6, 129.1, 129.5, 130.8 (Ph). Anal. Calcd $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.01; H, 5.22; N, 5.37; S, 13.48.

2-[(Methylsulfonyl)oxy]benzeneacetonitrile (2f).[13] To a solution of mandelonitrile (**1c**) (1.0 mL, 8.39 mmol) and Et_3N (3.2 mL, 25.2 mmol) in CH_2Cl_2 (30 mL) at 0°C, methanesulfonyl chloride (0.97 mL, 12,58 mmol) was added dropwise. The reaction was stirred at this temperature for 25 min, the solution was washed with water (1×40 mL and then 2×20 mL), the organic solvent was dried (Na_2SO_4) and evaporated. Column chromatography (4:1, hexane–ethyl acetate) yielded **2f** as a pale yellow syrup (1.19 g, 83%): IR (KBr) ν 1136, 1185 (SO_2O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.12 (s, 3 H, $MeSO_2$), 6.22 (s, 1 H, H-2), 7.49–7.59 (m, 5 H, C_6H_5). Anal. Calcd $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63; S, 15.17. Found: C, 51.11; H, 4.55; N, 6.70; S, 15.37.

4-Amino-5-methyl-5*H*-1,2-oxathiole 2,2-dioxide (3a). To a solution of **2a** (3.73 g, 24.9 mmol) in CH_3CN (50 mL) 60% of washed NaH (1.10 g, 27.4 mmol) was added, the reaction was stirred at room temperature for 1.5 h. Water (30 mL) was added and the solution was extracted with ethyl acetate (3×35 mL), the dried (Na_2SO_4) extracts were evaporated and the residue was purified by column chromatography (20:1, CH_2Cl_2–MeOH). The product was isolated as a pale yellow solid that was recrystallized from 1:1 hexane–ethyl acetate to give **3a** (0.739 g, 20%) as a white solid: mp 114–115°C; IR (KBr) ν 3475, 3385 (NH_2), 1665 (C=C(NH_2)R), 1300, 1155 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 1.47 (d, J=6.5 Hz, 3 H, Me), 5.12 (q, J=6.5 Hz, 1 H, H-5), 5.40 (s, 1 H, H-3), 6.67 (s, 2 H, NH_2); ^{13}C NMR (50 MHz, DMSO) δ 19.3 (CH_3), 78.1 (C-5), 84.3 (C-3), 157.8 (C-4); MS (70 eV) m/z 149 (M^+, 100), 134 (M^+-15, 65). Anal. Calcd $C_4H_7NO_3S$: C, 32.21; H, 4.73; N, 9.39; S, 21.49. Found: C, 32.11; H, 4.64; N, 9.09; S, 21.25.

4-Amino-3,5-dimethyl-5*H*-1,2-oxathiole 2,2-dioxide (3b). To a solution of **2b** (2.43 g, 14.9 mmol) in CH_3CN (20 mL) was added 60% NaH (0.655 g, 16.4 mmol) that had been washed with hexane prior to addition to remove the mineral oil. The mixture was stirred at room temperature for 1 h, water (30 mL) was added and the solution was extracted with ethyl acetate (3×30 mL). The extracts were dried (Na_2SO_4) and evaporated to give a yellow solid that was recrystallized from ethyl acetate–dichloromethane to yield **2b** (1.41 g, 58%) as a white solid: mp 162–164°C; IR (KBr) ν 3460, 3380 (NH_2), 1685 (HC═C–(NH_2)R), 1295, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 1.44 (d, J=6.4 Hz, 3 H, CH_3-C-5), 1.73 (s, 3 H, CH_3-C-3), 5.03 (q, J=6.4 Hz, 1 H, H-5), 6.28 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO) δ 5.4 (CH_3-3), 19.5 (CH_3-5), 77.4 (C-5), 90.8 (C-3), 151.1 (C-4); MS (70 eV) m/z 163 (M^+, 100), 148 (M^+-15, 38). Anal. Calcd $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; S, 19.65. Found: C, 36.77; H, 5.43; N, 8.86; S, 19.33.

4-Amino-5-ethyl-5*H*-1,2-oxathiole 2,2-dioxide (3c). To a solution of **2c** (3.50 g, 21.4 mmol) in CH_3CN (30 mL) was added 60% NaH (1.60 g, 40 mmol). The reaction was stirred at room temperature for 1.5 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3×25 mL), the organic extracts were dried (Na_2SO_4) and evaporated. Pure **3c** (1.74 g, 50%) was obtained by flash chromatography (2:1, ethyl acetate–hexane) as a yellowish amorphous solid: mp 65–67°C (hexane–dichloromethane); IR (KBr) ν 3470, 3460 (NH_2), 1660 (HC═C(NH_2)R), 1290, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 0.88 (t, J=7.3 Hz, 3 H, CH_3), 1.80–2.03 (m, 2 H, CH_2), 5.08 (dd, J=3.3 Hz, J=6.3 Hz, 1 H, H-5), 5.43 (s, 1 H, H-3), 6.66 (br s, 2 H, NH_2); ^{13}C NMR (50 MHz, DMSO) δ 7.6 (CH_3), 25.0 (CH_2), 82.6 (C-5), 85.4 (C-3), 156.0 (C-4); MS (70 eV) m/z 163 (M^+, 29), 134 (M^+-29, 52). Anal. Calcd $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; S, 19.65. Found: C, 36.55; H, 5.62; N, 8.37; S, 19.42.

4-Amino-5-ethyl-3-methyl-5*H*-1,2-oxathiole 2,2-dioxide (3d). To a solution of **2d** (0.51 g, 2.89 mmol) in CH_3CN (10 mL) was added slowly 60% NaH (0.14 g, 3.47 mmol). The reaction was stirred at room temperature for 20 min. Water (20 mL) was added and the mixture was extracted with dichloromethane (3×25 mL), the organic solvent was dried (Na_2SO_4) and was evaporated to give a residue that was purified by column chromatography (40:1–20:1, CH_2Cl_2–MeOH) to yield **3d** (0.429 g, 84%) as a colorless solid: mp 89–90°C (CH_2Cl_2–hexane); IR (KBr) ν 3440, 3365 (NH_2), 1670 (CH═C(NH_2)R), 1295, 1130 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 0.84 (t, J=7.2 Hz, 3 H, CH_3), 1.67–2.10 (m, 2 H, CH_2), 1.74 (s, 3 H, Me-C-3), 4.99–5.15 (br m, 1 H, H-5), 6.23 (br s, 2H, NH_2); ^{13}C NMR (50 MHz, DMSO) δ 5.4 (CH_3-C-5), 7.6 (CH_3CH_2), 25.0 (CH_3CH_2), 81.7 (C-5), 92.0 (C-3), 149.1 (C-4); MS (70 eV) m/z 177 (M^+, 52), 146 (M^+-29, 48). Anal. Calcd $C_6H_{11}NO_3S$: C, 40.67; H, 6.26; N, 7.90; S, 18.09. Found: C, 40.48; H, 6.01; N, 7.78; S, 18.12.

4-Amino-5-ethyl-3-phenyl-5*H*-1,2-oxathiole 2,2-dioxide (3e). 60% NaH (40 mg, 1.0 mmol) was added slowly to a solution of **2e** (217 mg, 0.91 mmol) in CH_3CN (15 mL). After 5 min at room temperature, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried (Na_2SO_4) and evaporated, the residue was purified by flash chromatography (2:1, hexane–ethyl acetate and then 20:1 CH_2Cl_2–MeOH) to give **3e** (196.5 mg, 91%) as a white solid: mp 123–125°C (ethanol–water); IR (KBr) ν 2440, 3360 (NH_2), 1660 (CH═C(NH_2)R), 1300, 1160 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 0.93 (t, J=7.3 Hz, 3 H, CH_3), 1.18–2.15 (m, 2 H, CH_2), 5.20 (dd, J=3.3 Hz, J=6.3 Hz, 1 H, H-5), 6.80 (br s, 2 H, NH_2), 7.20–7.60 (m, 5 H, Ph); ^{13}C NMR (50 MHz, DMSO) δ 7.6 (CH_3), 25.3 (CH_2), 81.1 (C-5), 126.9, 127.1, 129.0 (Ph), 128.0 (C-3), 149.6 (C-4); MS (70 eV) m/z 239 (M^+, 100). Anal. Calcd $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.18; H, 5.33; N, 5.92; S, 13.23.

2-Aminobutanenitrile (4b).[21] Propanal (4.0 mL, 55.4 mmol) was added to a solution of KCN (3.77 g, 58.21 mmol), NH_4Cl (3.26 g, 61.0 mmol) and 30% NH_4OH (6.50 mL, 55.4 mmol) in water (30 mL), the reaction was stirred at room temperature for 17 h. The mixture was extracted with dichloromethane (3×45 mL), the solution was dried (Na_2SO_4) and evaporated to give impure **4b** as an unstable orange oil (4.01 g, approximately 86%). This intermediate was used without further purification.

2-(Methylamino)-butanenitrile (4c).[22] A solution of propanal (2.0 mL, 27.7 mmol), methylamine hydrochloride (2.43 g, 36.0 mmol) and KCN (1.99 g, 30.5 mmol) in water (20 mL) was stirred at room temperature for 4 h. The solution was extracted with dichloromethane (3×30 mL), the solvent was dried (Na_2SO_4) and the solvent was removed to give crude **4c** (2.15 g, 79%) as a pale yellow oil. This product was used directly for the synthesis of **6a**.

3-Methyl-2-(methylamino)-butanenitrile (4d).[23] To a solution of methylamine hydrochloride (2.70 g, 40.0 mmol) in water was added 2-methylpropanal (3.0 mL, 33.0 mmol), the biphasic mixture was stirred rapidly for 10 min. A solution of KCN (2.81 g, 43.23 mmol) in water (15 mL) was added slowly over 25 min, during the addition of this solution the reaction became warm and cloudy. Upon the addition of all of the solution of KCN the reaction was stirred at room temperature for 2 h, the solution was extracted with dichloromethane (3×30 mL), the organic layer was dried (Na_2SO_4) and evaporated to yield crude **4d** (3.48 g, 94% approx.) as a colorless oil: IR (KBr) ν 3350 (NH), 2225 (CN), 1390 and 1370 ($(CH_3)_2C$) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, J=6.8 Hz, 6 H, 2×CH_3), 1.95–1.98 (m, 1 H, H-3), 2.54 (s, 3 H, CH_3N), 3.24 (d, J=5.8 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 19.1 (2×CH_3), 31.2 (CH_3N), 34.5 (C-3), 59.3 (C-2), 119.1 (CN). Anal. Calcd $C_6H_{12}N_2$: C, 64.24; H, 10.78; N, 24.97. Found: C, 64.56; H, 10.53; N, 24.69.

***N*-(Cyanomethyl)-methanesulfonamide (5a).**[24] A suspension of commercial aminoacetonitrile bisulfate **4a** (2.0 g, 13.06 mmol) was added to a mixture of triethylamine (6.60 mL, 52.2 mmol) and dichloromethane (30 mL). The mixture was stirred at room temperature for 10 min to convert the bisulfate to its soluble free base. The mixture was cooled to 0°C, methanesulphonyl chloride (1.2 mL, 15.67 mmol) was added dropwise and the reaction was

stirred for 1.5 h at room temperature. Hexane (30 mL) was added and the mixture was filtered over Celite, the solvent was evaporated and the residue was purified by flash chromatography (1:1, hexane–ethyl acetate) to yield **5a** (0.586 g, 31%) as a colorless solid: mp 70–71°C (from $CHCl_3$); IR (KBr) ν 3300 (NH), 2240 (CN weak), 1360, 1160 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 3.00 (s, 3 H, CH_3SO_2N), 4.17 (s, 2 H, NCH_2CN), 8.0 (br s, 1 H, NH_2). Anal. Calcd $C_3H_6N_2O_2S$: C, 26.86; H, 4.51; N, 20.88; S, 23.90. Found: C, 26.54; H, 4.37; N, 20.58; S, 23.72.

(*N*-Benzyl, *N*-cyanomethyl)-methanesulfonamide (5b). Benzyl bromide (0.38 mL, 3.2 mmol) was added to a refluxing mixture of **5a** (286 mg, 2.13 mmol) and K_2CO_3 (0.89 g, 6.40 mmol) in dry CH_3CN (20 mL). The reaction was refluxed for 1 h, was cooled and filtered, the solvent was evaporated and the residue was purified by flash chromatography (3:1, hexane–ethyl acetate) to give **5b** (446 mg, 93%) as crystals: mp 70–71°C; IR (KBr) ν 2240 (CN weak), 1360, 1160 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.05 (s, 3 H, CH_3SO_2N), 4.01 (s, 2 H, NCH_2CN), 4.44 (s, 2 H, NCH_2Ph), 7.37 (s, 5 H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.1 (CH_2CN), 37.9 (CH_3SO_2N), 50.8 (CH_2Ph), 114.9 (CN), 128.6, 128.8, 129.1, 122.13 (Ph). Anal. $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49; S; 14.29. Found: C, 53.75; H, 5.22; N, 12.37; S; 14.12.

***N*-(1-Cyano-1-propyl)-methanesulfonamide (5c).** Methanesulfonyl chloride (1.09 mL, 14.3 mmol) was added to a solution of crude **4b** (1.00 g, 11.9 mmol, theor.) and Et_3N (3.0 mL, 23.8 mmol) in CH_2Cl_2 (20 mL) at 0°C. The reaction was allowed to reach room temperature over 1.5 h, was filtered over Celite and the solvent was evaporated. Chromatography (3:1–1:1, hexane–ethyl acetate) yielded **5c** (0.70 g, 36%) as a yellow syrup: IR (KBr) ν 3300 (NH), 2240 (CN weak), 1360, 1160 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, J=7.3 Hz, 3 H, H-4), 1.84 (qt, J=7.3 Hz, 2 H, H-3), 3.08 (s, 3 H, CH_3SO_2N), 4.23 (dt, J=7.3, 9.0 Hz, 1H, H-2), 5.03 (br d, J=9.0 Hz, 1H, NH). Anal. $C_5H_{10}N_2O_2S$: C, 37.02; H, 6.21; N, 17.27; S, 19.76. Found: C, 37.14; H, 6.18; N, 17.44; S, 19.97.

[*N*-Benzyl, *N*-(1-cyano-1-propyl)]-methanesulfonamide (5d). Benzyl bromide (367 μL, 3.09 mmol) was added to a refluxing mixture of **5c** (436 mg, 2.69 mmol) and K_2CO_3 (742 mg, 5.37 mmol) in CH_3CN (20 mL). The reaction was refluxed for 2 h, was cooled, filtered and evaporated to give a residue that was purified by flash chromatography (3:1, hexane–ethyl acetate) yielding **5d** (548 mg, 81%) as a yellow syrup that solidified on standing: mp 60–62°C; IR (KBr) ν 1350, 1170 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J=7.3 Hz, 3 H, H-4), 1.56–1.59 (m, 2 H, H-3), 2.93 (s, 3 H, CH_3SO_2N), 4.68–4.72 (t, J=7.2 Hz, 1 H, H-2), 4.23 and 4.72 (2×d, J=15.0 Hz, 2 H, CH_2Ph), 7.35–7.57 (m, 5 H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.3 (C-4), 26.8 (C-3), 38.3 (CH_3SO_2N), 50.0, 51.9 (C-3, CH_2Ph), 117.0 (CN), 128.3, 128.8, 135.9 (Ph). Anal. Calcd $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 57.06; H, 6.22; N, 11.24; S, 12.57.

***N*-(1-Cyano-1-propyl)-ethanesulfonamide (5e).** Ethanesulfonyl chloride (1.15 mL, 12.2 mmol) was added dropwise at 0°C to a solution of crude **4b** (0.93 g, 11.0 mmol theor.) and Et_3N (4.25 mL, 33.2 mmol) in dichloromethane (30 mL). The reaction was allowed to reach room temperature over 2 h, ethyl acetate (30 mL) was added and the mixture was filtered over Celite. Evaporation of the solvent gave a residue that was purified by column chromatography (3:1–1:1, hexane–ethyl acetate) to yield **5e** as a yellow oil (687 mg, 35%): IR (KBr) ν 3280 (NH), 2250 (CN, weak), 1360, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (t, J=7.3 Hz, 3 H, $CH_3CH_2SO_2$), 1.41 (t, J=7.5 Hz, 3 H, H-4), 1.91–1.94 (m, 2 H, H-3), 3.20 (q, J=7.3 Hz, 2 H, $CH_3CH_2SO_2N$), 4.28 (t, J=6.6 Hz, 1 H, H-2), 5.19 (br s, 1 H, NH). Anal. $C_6H_{12}N_2O_2S$: C, 40.89; H, 6.86; N, 15.90; S, 18.19. Found: C, 40.76; H, 6.52; N, 15.85; S, 18.01.

[*N*-Benzyl, *N*-(1-cyano-1-propyl)]-ethanesulfonamide (5f). To a mixture of **5e** (290 mg, 1.64 mmol) and K_2CO_3 (455 mg, 3.29 mmol) in CH_3CN (15 mL) was added benzyl bromide (293 μL, 2.47 mmol). The mixture was refluxed for 2 h, cooled, filtered and evaporated to give a residue that was purified by flash chromatography (3:1, hexane–ethyl acetate) to give **5f** (386 mg, 88%) as a colourless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J=7.3 Hz, 3 H, $CH_3CH_2SO_2$), 1.39 (t, J=7.5 Hz, 3 H, H-4), 1.54–1.57 (m, 2 H, H-3), 2.98 (q, J=7.3 Hz, 2 H, $CH_3CH_2SO_2$), 4.69 (t, J=7.2 Hz, 1 H, H-2), 4.27 and 4.75 (d, d, J=15.0 Hz, 2 H, CH_2Ph), 7.25–7.50 (m, 5 H, Ph). Anal. Calcd $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.57; H, 6.69; N, 10.47; S, 12.12.

[*N*-(1-Cyano-2-methylpropyl), *N*-methyl]-ethanesulfonamide (5g). Ethanesulfonyl chloride (1.90 mL, 15 mmol) was added dropwise to a solution of Et_3N (7.24 mL, 40.12 mmol) and **4d** (1.50 g, 13.37 mmol) in CH_2Cl_2 (30 mL) at 0°C. The reaction was stirred for 30 min, the solution was washed with water (3×10 mL), the solution was dried (Na_2SO_4) and evaporated. Purification by chromatography (3:1, hexane–ethyl acetate) gave **5g** (2.64 g, 97%) as a yellowish oil: IR (KBr) ν 2240 (weak, CN), 1340, 1145 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 and 1.10 (2 d, J=6.6, 5.6 Hz, 2×3 H, $(CH_3)_2CH$), 1.39 (t, J=7.4 Hz, 3 H, $CH_3CH_2SO_2$), 2.12–2.17 (m, 1 H, H-3), 2.90 (s, 3 H, CH_3N), 3.05 (q, J=7.4 Hz, 2 H, $CH_3CH_2SO_2$), 4.29 (d, J=7.0 Hz, 1 H, H-2). Anal. Calcd. $C_8H_{16}N_2O_2S$: C, 47.04; H, 7.89; N, 13.71; S, 15.69. Found: C, 47.27; H, 7.65; N, 13.86; S, 15.55.

[*N*-(1-Cyano-2-methylpropyl), *N*-methyl]-benzenemethanesulfonamide (5h). To a solution of **4d** (210 mg, 1.87 mmol) and Et_3N (0.85 mL, 4.69 mmol) in dichloromethane (20 mL) was added α-toluenesulfonyl chloride (462 mg, 2.42 mmol), the mixture was stirred at room temperature for 23 h. Water (20 mL) was added and the solution was extracted with CH_2Cl_2 (3×35 mL), the organic extracts were dried (Na_2SO_4) and evaporated. Column chromatography (4:1, hexane–ethyl acetate) gave **5h** (275.7 mg, 55%): oil; IR (KBr) ν 2240 (weak, CN), 1340, 1145 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 and 1.11 (2 d, J=6.6, 5.6 Hz, 2×3 H, 2×CH_3), 2.00–2.02 (m, 1 H, H-3), 2.73 (s, 3 H, CH_3N), 4.15 (d, J=7.0 Hz, 1 H, H-2), 4.28 (s, 2 H, CH_2Ph), 7.40 (m, 5 H, Ph). Anal. Calcd $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S 12.04. Found: C, 58.57; H, 6.74; N, 10.34; S, 12.27.

[*N*-(1-Cyano-1-propyl), *N*-methyl]-cyanomethylenesulfonamide (5j). To a solution of **4d** (247 mg, 2.20 mmol) in CH_2Cl_2 (10 mL) was added cyanomethylenesulfonyl chloride[14] (335 mg, 2.40 mmol). Pyridine (0.43 mL, 5.40 mmol) was added and the solution immediately became dark brown, the mixture was stirred at room temperature for 18 h. Ethyl acetate (10 mL) was added and the mixture was filtered over Celite, evaporation of the solvent gave a residue that was purified by flash chromatography (2:1–1:1, hexane–ethyl acetate) to yield **5j** (164.4 mg, 35%) as a yellow syrup that crystallized upon standing: mp 68–70°C; IR (KBr) ν 2260 (weak CN), 1370 and 1350 $(CH_3)_2C$), 1340, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 and 1.05 (2 d, J=6.6 Hz, 2×3 H, $(CH_3)_2CH$), 2.13–2.16 (m, 1 H, H-3), 3.09 (s, 3 H, CH_3N), 4.06 (s, 2 H, SO_2CH_2CN), 4.37 (d, J=7.0 Hz, 1 H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2 and 19.1 (2×CH_3), 30.0 (CH_3N), 31.8 (C-3), 39.8 (SO_2CH_2CN), 56.57 (C-2), 115.76 (SO_2CH_2CN). Anal. $C_8H_{13}N_3O_2S$: C, 44.64; H, 6.09; N, 19.52; S, 14.89. Found: C, 44.32; H, 6.22; N, 19.34; S, 14.68.

4-Amino-5-cyano-3-ethyl-5*H*-2,3-dihydroisothiazole 1,1-dioxide (6a). To a solution of **4c** (410 mg, 4.18 mmol) in CH_2Cl_2 (10 mL) was added cyanomethylenesulfonyl chloride[14] (700 mg, 5.02 mmol). Pyridine (1.01 mL, 12.54 mmol) was added and the solution immediately became dark brown, the mixture was stirred at room temperature for 18 h. Ethyl acetate (30 mL) was added and the mixture was filtered over Celite, evaporation of the solvent gave a residue that was purified by flash chromatography (3:1–2:1, hexane–ethyl acetate) to yield the crude sulfonamide intermediate **5i** (318 mg, 35%) as a brownish syrup. Purification of this compound was not possible as it cyclized spontaneously during chromatography, thus all samples were contaminated with **6a**.

To a solution of this product (286 mg, 1.42 mmol) in CH_3CN (10 mL) was added DBU (110 μL, 0.737 mmol), the mixture was stirred at room temperature for 2 h. The solvent was evaporated and column chromatography (20:1–10:1, CH_2Cl_2–MeOH) yielded **6a** as a colorless solid (175 mg, 61%): mp 208–209°C (shiny white plates from ethanol); IR (KBr) ν 3380, 3235 (NH), 2220 (CN strong), 1670, 1615 (NC–C=C–(NH_2)R), 1285, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, acetone) δ 0.90 (t, J=7.3 Hz, 3 H, CH_3), 1.97–2.00 (m, 2 H, CH_2), 2.71 (s, 3 H, CH_3N), 4.12 (t, J=4.2 Hz, 1 H, H-3), 7.62 (br s, 2 H, NH_2); ^{13}C NMR (50 MHz, acetone) δ 7.4 (CH_3), 23.9 (CH_2), 31.2 (CH_3N), 65.0 (C-3), 80.1 (C-5), 111.4 (CN), 164.5 (C-4). Anal. Calcd $C_7H_{11}N_3O_2S$: C, 41.78; H, 5.51; N, 20.88; S, 15.93. Found: C, 41.54; H, 5.38; N, 20.77; S, 15.87.

4-Amino-5-cyano-3-(1′-methylethyl)-5*H*-2,3-dihydroisothiazole 1,1-dioxide (6b). A solution containing **5j** (42.5 mg, 0.197 mmol) and DBU (15 μL, 0.1 mmol) in CH_3CN (3 mL) was stirred at room temperature for 3 h. The solution was evaporated and the residue was submitted to column chromatography (20:1, CH_2Cl_2–MeOH) to yield **6b** (32.8 mg, 77%) as a white solid: mp 230–231°C (plates from MeOH–acetone); IR (KBr) ν 3380, 3235 (NH), 2220 (CN strong), 1670, 1615 (NC–C=C–(NH_2)R), 1285, 1150 (SO_2) cm^{-1}; ^1H NMR (200 MHz, acetone) δ 0.92 and 1.14 (2 d, 2×3H, J=6.8 Hz, 2×$(CH_3)_2CH$), 2.33–2.36 (m, 1 H, $(CH_3)_2CH$), 2.80 (s, 3 H, CH_3N), 4.04 (d, 1 H, J=2.8 Hz, H-3), 7.50 (br s, 2 H, NH_2); ^{13}C NMR (50 MHz, acetone) δ 15.5 and 20.4 (2×CH_3, $CH(CH_3)_2$), 33.1 (CH_3N), 36.4 ($CH(CH_3)_2$), 71.1 (C-3), 80.1 (C-5), 111.4 (CN), 164.7 (C-4). Anal. Calcd $C_8H_{13}N_3O_2S$: C, 44.64; H, 6.09; N, 19.52; S, 14.89. Found: C, 44.42; H, 6.15; N, 19.63; S, 14.71.

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