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Reactivity of the 4-Amino-5*H*-1,2-Oxathiole-2,2-Dioxide Heterocyclic System: A Combined Experimental and Theoretical Study

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Abstract: The reactivity of the 4-amino-5*H*-1,2-oxathiole-2,2-dioxide (or β-amino-γ-sultone) heterocyclic system has scarcely been studied. Here we describe the reactivity of this system towards electrophiles and amines on readily available model substrates differently substituted at the C-5 position. A variety of C-electrophiles, carbonyl electrophiles (such as acyl chlorides, isocyanates, or aldehydes) and halogen or nitrogen electrophiles have been explored. Both the C-3 and 4-amino positions of the β-amino-γ-sultone system are able to undergo electrophilic reactions, and the reaction products depend on the electrophile used and on the reaction conditions. On the other hand, nucleophilic attack of amines occurs at the C-4 position of the β-amino-γ-sultone system only in spiranic substrates bearing alicyclic substituents at the C-5 position. A comparative computational study between spiranic and non-spiranic substrates suggests that conformational changes, undergone on intermediate compounds, account for the observed reactivity differences. Moreover, these conformational changes seem to bring about an increase of electron density on the N-4 and C-3 atoms of the enaminic system, and a possible enhancement in the reactivity of spiranic substrates towards electrophiles in the presence of amines. Experimental data consistent with this predicted enhanced reactivity is also presented.

Keywords: density functional calculations · heterocycles · reactive intermediates · spiro compounds · sultones

Introduction

Sultones are versatile heterocyclic intermediates, the chemistry, industrial applications, and biological properties of which continue to be of interest.[1] Even though recent chemical literature on saturated γ-sultones has been described,[2] research on the chemistry of α,β-unsaturated-γ-sultones,[3] and particularly of β-amino-substituted representatives of this family, is much more scarce. The 4-amino-5*H*-1,2-oxathiole-2,2-dioxide (or β-amino-γ-sultone) heterocyclic system, first reported by us in 1988,[4] was generated by treatment of α-mesyloxynitriles of sugars under non-nucleophilic basic conditions. The mechanism involves deprotonation of the alkylsulfonate moiety at the α-position, in a basic medium, and attack of the carbanion, thus generated, on the cyano group through an intramolecular aldol-type cyclocondensation to give, eventually, the cyclic enamine system. This unexpected synthetic event (the expected reaction would have been a β-elimination to leave a cyano group attached to a double bond) was later extended to other α-mesyloxynitriles of sugars,[5] and non-carbohydrate templates (adamantane derivatives).[6] We also reported the application of this reaction to nucleoside templates, which led to the discovery of a unique class of potent and specific anti-HIV-1 agents called TSAO derivatives.[7–9] This aldol-type cyclo-condensation was later renamed by other researchers as a CSIC reaction (carbanion-mediated sulfonate intramolecular cyclisation reaction) and further used with other alkanesulfonate or alkanesulfonamide substrates.[10–12]

The potentially rich chemical reactivity embodied in the β-amino-γ-sultone heterocyclic ring has been investigated, although not in detail.[10a] Various synthetic studies for the

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800433, and contains general experimental methods, synthesis and characterisation of compounds **4b**, **5b**, **6**, **10b**, **13**, **21**, **22**, **24**, **27**, **28**, **30a**, **30b**, **31b**, **32b**, **37**–**42**, **44**–**46**, **48**–**51**, and **53**, plus an additional figure showing the general structure of TSAO nucleosides.

direct and selective functionalisation of the C-3 or the amino positions of the enamine system on TSAO compounds have been performed.[13,14] However, the presence of *tert*-butyldimethylsilyl groups (TBDMS) at positions 2′ and 5′, sensitive to basic and acid media, respectively, but essential for the antiviral efficacy of the TSAO compounds, restricted the selection of smooth reaction conditions compatible with such groups. The corresponding β-keto-γ-sultone, obtained by hydrolysis,[6,10a] has been transformed to β-amino and β-keto sulfonic acids by reductive opening of the ring.[11b] Moreover, chloroformylation of the β-keto-γ-sultone system led to unsaturated β-chloro-α-formyl-γ-sultone derivatives, which are useful intermediates for the synthesis of heterocyclic compounds.[15] Finally, opening of the 4-amino-5*H*-1,2-oxathiole-2,2-dioxide system on sugar derivatives has also been carried out with a nucleophilic base such as methanolic sodium methoxide.[5]

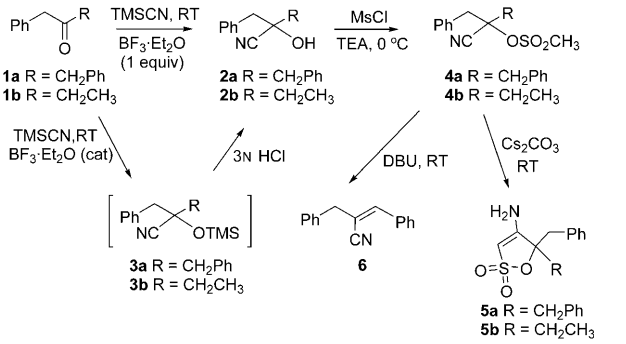
In this current work we describe the chemical reactivity of the enamine system of the β-amino-γ-sultone heterocyclic ring on easily available simple model substrates, which would allow exploration of a wider range of reaction conditions than in TSAO derivatives. The behaviour of this system towards electrophiles of different nature and amines has been investigated. Our results revealed that the reactivity towards amines is highly dependent on the nature of the C-5 substituents of the substrate. We also discuss the experimentally observed chemical reactivity differences in the light of molecular calculations. This study is able to justify the experimental results based on electronic and geometrical features of reactive and intermediate compounds. A further analysis of these intermediates suggests an enhanced reactivity of spiranic substrates towards electrophiles, in the presence of bases, in comparison with non-spiranic substrates. Experimental data consistent with this predicted enhancement of reactivity is also presented.

Results and Discussion

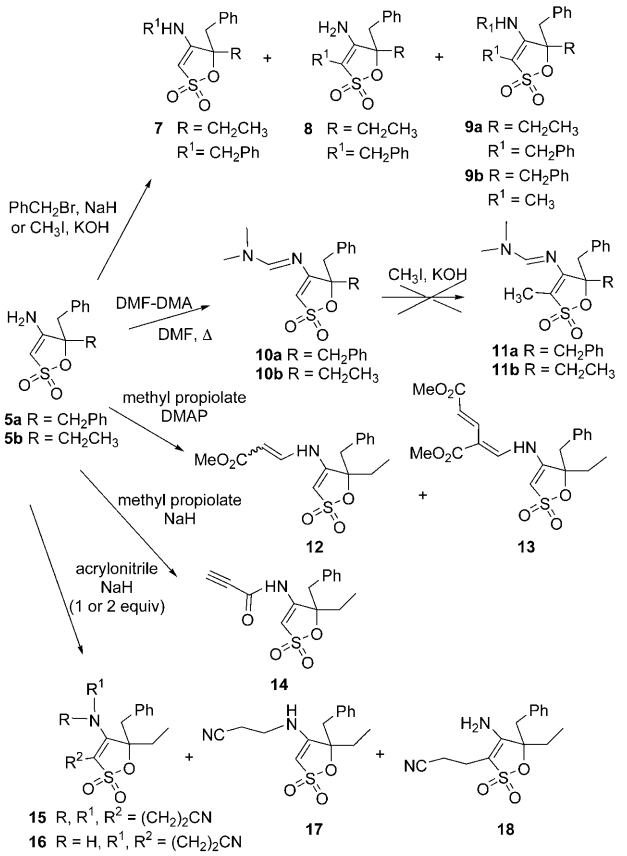
The β-amino-γ-sultone derivatives **5a**,**b** were selected as simple and readily available substrates for our studies (Scheme 1). We first focused on achieving optimal reaction conditions for the synthesis of the dibenzyl derivative **5a**, which involved cyanohydrine formation from the corresponding commercially available ketones, followed by mesylation and final ring closure with an appropriate base. Thus, reaction of 1,3-diphenyl-2-propanone (**1a**) with sodium cyanide and sodium hydrogencarbonate in ether/water, according to previously described conditions,[5,8,10a] afforded the cyanohydrine **2a** (40%) together with unreacted starting material (40%; Scheme 1). Better yields were obtained through the TMS-protected cyanohydrines procedure.[16,17] Thus, treatment of **1a** with trimethylsilyl cyanide in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$, followed by deprotection of the trimethylsilyl cyanohydrine **3a** with 3N hydrochloric acid, afforded the cyanohydrine **2a** in 70% yield. Further improvement of this reaction was achieved when equimolecular amounts of $BF_3{\cdot}Et_2O$ were used. Under these conditions the two-step method could be performed in a one-pot procedure and the cyanohydrine **2a** was obtained in higher yields (90%). Reaction of **2a** with mesyl chloride (slowly added at 0°C) in dichloromethane, with triethylamine as base at room temperature, gave the desired alkyl sulfonate derivative **4a** in low yield (25%) and the ketone derivative **1a** (40%), used as starting material. Conversion of the cyanohydrine back to the ketone material could be avoided when the mesyl chloride was slowly added at −20°C and the reaction was then stirred at 0°C. The desired alkyl sulfonate derivative **4a** was then obtained in 80% yield. The cyclisation-base step in TSAO derivatives is usually carried out either with Cs_2CO_3 or DBU.[7–9] Compound **4a** failed to cyclise by using DBU as the base. Instead, β-elimination of the tertiary mesylate group was observed (compound **6**,[18] Scheme 1). However, the β-amino-γ-sultone derivative **5a** was readily obtained when Cs_2CO_3 or NaH were used as bases (80% or 62% yield, respectively).

The synthesis of β-amino-γ-sultone derivative **5b**, bearing a benzyl and an ethyl substituent at the C-5 position, was carried out in a similar way, using these conditions and starting from commercially available 1-phenyl-2-butanone **1b** (Scheme 1). The ^{1}H NMR spectra of compounds **5a**,**b** showed the presence of two singlets at 6.33 and 5.21 ppm for **5a**, and at 6.19 and 5.40 ppm for **5b**. The high-field signals disappeared on rapid exchange with D_2O and were assigned to the NH_2 group. The downfield singlets that disappeared on slow exchange with D_2O were assigned to H-3. The slow exchange could be due to an imine-enamine tautomeric equilibrium.[5]

The β-amino-γ-sultone ring has two electron-rich centres at C-3 and 4-amino, respectively. We first examined the reactivity of the model β-amino-γ-sultone derivatives **5a**,**b** towards C-electrophiles such as alkyl halides. Thus, reaction of **5b** with benzyl bromide in the presence of NaH at room temperature afforded the 4-*N*- and 3-*C*-benzylated derivatives **7** (21%) and **8** (10%) together with the *N*,*C*-dialkylated compound **9a** (15%) and unreacted starting material (Scheme 2). Longer reaction times and increasing amounts of the electrophile and the base (1 or 2 additional equivalents) afforded, exclusively, the *N*,*C*-dialkylated derivative **9a** in a 51% yield. Similarly, reaction of **5b** with methyl



Scheme 1.



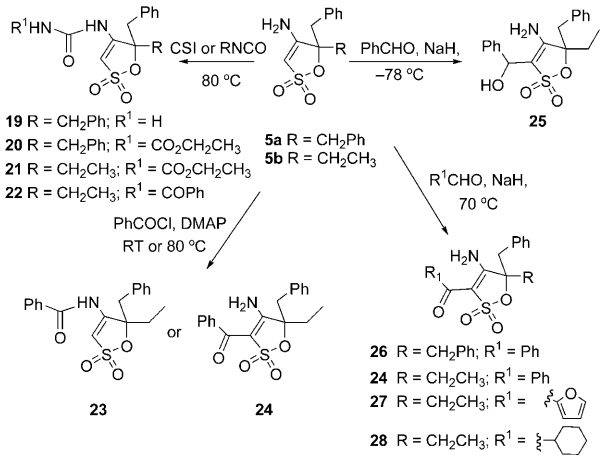
Scheme 2.

iodide in the presence of KOH also afforded the *N*,*C*-dialkylated derivative **9b** in 47% yield. These results were similar to those obtained in TSAO nucleosides.[13] We next studied the reaction of **5a** with dimethylformamide dimethylacetal to give the protected amino compound, and its reaction with alkyl halides in order to alkylate regioselectively the C-3 position of the sultone ring. The 4-dimethylaminomethylenamino derivatives **10a**,**b** were easily prepared in excellent yields (97%) by the condensation reaction of **5a**,**b** with an excess of dimethylformamide dimethylacetal.[19] However, all attempts to alkylate **10a**,**b** with methyl iodide in the presence of different bases (NaH or KOH) were unsuccessful and unreacted starting material was recovered, in spite of the expected increased nucleophilicity of C-3 due to the electron-donating effect of the dimethylaminomethylenamino substituent at C-4.

Next, we turned out our attention to the reaction of the model substrates with α,β-unsaturated reagents (Michael acceptors) as C-electrophiles. It appears that in this case alkylation of the enamine system, in the presence of DMAP, takes place exclusively through the amine, albeit in low yields. Thus, treatment of sultone **5b** with 1.2 equivalents of methyl propiolate in acetonitrile in the presence of DMAP at 0°C for two hours gave a 10:1 mixture of *E*/*Z* Michael adducts **12** (Scheme 2) in 17% yield, together with unreacted starting material (45%). When this reaction was carried out at room temperature overnight, a mixture of compounds **12** (17%), **13** (10%) and unreacted starting material (40%) was obtained. Formation of compound **13** could be explained by a second Michael addition of enamine **12** to methyl propiolate. Prolonged reaction time or increased equivalents of the electrophile and of the base led to the decomposition of the starting material, but did not increase the yields of the products. Interestingly, when the reaction between **5b** and methyl propiolate was carried out in the presence of NaH as the base, the *N*-acylated derivative **14** was obtained in 40% yield.

To avoid acylation of the 4-amino group in the presence of NaH, methyl propiolate was replaced by acrylonitrile as the Michael acceptor. When model sultone **5b** was reacted with two equivalents of acrylonitrile in the presence of NaH at room temperature for one hour, mixtures of the *N*,*C*-di and the tri-Michael adducts **15** and **16** were isolated (Scheme 2). Reduced amounts of acrylonitrile and base (1 equiv) afforded mixtures of the *N*- and *C*-monoalkylated **17** and **18** and the *N*,*C*-dialkylated compound **16** (Scheme 2). Polyalkylation of the enamine system could be explained by the higher reactivity of the Michael acceptor (acrylonitrile vs methyl propiolate).

Reaction of the model β-amino-γ-sultone derivatives **5a**,**b** with carbonyl electrophiles, such as isocyanates, occurs exclusively at the 4-amino group of the enamine system in good yields. Thus, reaction of **5a** with chlorosulfonyl isocyanate in acetonitrile, followed by treatment with aqueous $NaHCO_3$, gave the 4-unsubstituted ureido derivative **19** in 46% yield (Scheme 3). Similarly, reaction of **5a**,**b** with an excess of ethoxycarbonyl or benzoyl isocyanate, in dry acetonitrile at 80°C, afforded the corresponding 4′′-*N*-acyl substituted ureido derivatives **20** (93%), **21** (60%), and **22** (81%) in good yields.



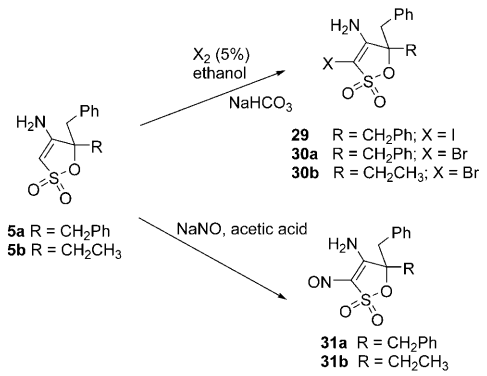
Scheme 3.

Treatment of compound **5b** with an excess of benzoyl chloride and DMAP as base in acetonitrile afforded the *N*-benzoyl derivative **23** in 71% yield (Scheme 3) after a pro-

longed reaction time (4 days) at room temperature. When this reaction was carried out in a pressure reaction vessel at 80 °C (general *N*-acylation conditions used in TSAO nucleoside derivatives),[14] the initially observed *N*-acyl group of **23** underwent migration to the enaminic C-3 carbon to give the C-acylated product **24** after three hours, in good yield (69 %). It should be noted that *N*-acylation of the β-amino-γ-sultone heterocyclic system at room temperature or C-acylation with acyl chlorides has never been observed previously in TSAO nucleoside derivatives.[14]

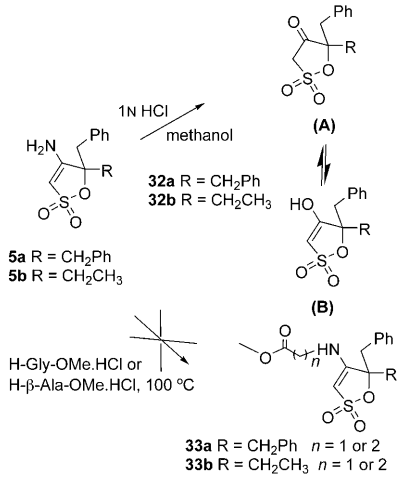
Other carbonyl electrophiles such as aldehydes (previously unexplored in TSAO nucleoside substrates) react with model sultone derivatives **5a**,**b** exclusively at the C-3 position of the enamine system (Scheme 3). Reaction of **5b** with benzaldehyde in dry THF in the presence of NaH at low temperature (−78 °C) afforded the 3-hydroxyphenylmethyl derivative **25** in low yield. Interestingly, when **5a**,**b** was reacted with benzaldehyde under similar conditions at 70 °C, the 3-benzoyl derivatives **26** and **24** were obtained in 88 and 77 % yield, respectively. Similarly, reaction of **5b** with 2-furaldehyde and cyclohexanaldehyde at 70 °C afforded the 3-acyl derivatives **27** and **28** in good yields (74 and 73 %, respectively). However, reaction of **5a**,**b** with acetaldehyde, propanaldehyde or unsaturated aldehydes, such as crotonaldehyde, failed in all cases, and only decomposition of the starting material was observed.

We next investigated the behaviour of the model substrates **5a**,**b** towards other electrophiles, such as halogen or nitrogen electrophiles (Scheme 4). Compounds **5a**,**b** reacted with halogen electrophiles, also exclusively at the C-3 position of the enamine system, in good yields. Bromo and iodo substituents were easily introduced by using Johnson's conditions,[20] which involves iodine in basic medium. Thus, treatment of **5a** with iodine in ethanol, and sodium bicarbonate as base, afforded the 3-iodo derivative **29** in 70 % yield. Similarly, reaction of **5a**,**b** with bromine in ethanol yielded the 3-bromo derivatives **30a**,**b** in excellent yields (98 and 95 %, respectively). On the other hand, nitrosation of **5a**,**b** with sodium nitrite in acetic acid at 0 °C gave the purple 3-nitroso derivatives **31a**,**b** in 81 and 61 % yield, respectively (Scheme 4). These 3-functionalised derivatives could be considered as useful intermediates for further functionalisation of this heterocycle.



Scheme 4.

Modifications at the 4-position of the β-amino-γ-sultone heterocyclic system, which have been previously reported to work smoothly in this system, such as acid hydrolysis of the enamino system,[6,10a,12] or substitution of this amino group by other amines through transamination reactions[14] were next addressed in our substrates (Scheme 5). In good agreement with previous results, hydrolysis of compounds **5a**,**b** with 1 N HCl in methanol afforded the expected β-keto-γ-sultone derivatives **32a**,**b** (Scheme 5) in good yields (85 and 76 %, respectively). Alternative methods for the synthesis of the β-keto-γ-sultone heterocyclic system involved cyclisation of α-(carboxyethyl)alkyl alkanesulfonates.[21]

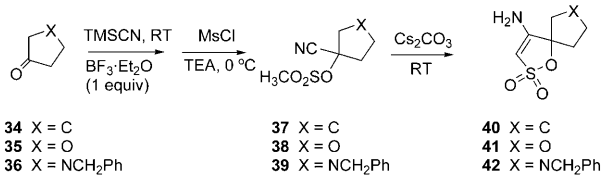


Scheme 5.

^{1}H and ^{13}C NMR spectra of compounds **32a**,**b** revealed that they exist in solution in the keto (**A**) or enol (**B**) forms depending on the choice of solvent. In $CDCl_3$, the ^{1}H NMR spectra of **32a**,**b** showed the disappearance of the singlets assigned to the 4-NH_2 and the H-3, and the presence of a new AB system at $\delta = 2.99$ and 3.23 ppm, corresponding to the H-3 of the keto form **A**. In ^{13}C NMR, the chemical shifts for the C-4 ketone carbonyl are at $\delta = 200.6$ and 200.8 ppm, which are typical values for ketone carbonyls. However, in [D_6]DMSO, the ^{1}H NMR spectra of **32a**,**b** showed a broad singlets at $\delta = 12.75$ and 12.84 ppm, respectively, exchangeable with D_2O, which were assigned to the hydroxyl protons of the corresponding enol tautomers (**B**). The singlets at $\delta =$ 5.86 ppm for **32a** and $\delta = 6.03$ ppm for **32b** were assigned to the H-3 vinyl protons of the corresponding enol tautomers. In ^{13}C NMR, the enolic C-4 carbon appears at $\delta = 166.2$ ppm for **32a** and $\delta = 166.2$ ppm for **32b**. These results indicate that in [D_6]DMSO, compounds **32a**,**b** exist in enol form.

However, in contrast with TSAO derivatives,[14] transamination reactions of **5a**,**b** with an excess of H-Gly-OMe.HCl or H-β-Ala-OMe.HCl as amines, heated in methanol under reflux in a sealed tube for several days were unsuccessful, and unreacted starting material was recovered (Scheme 5).

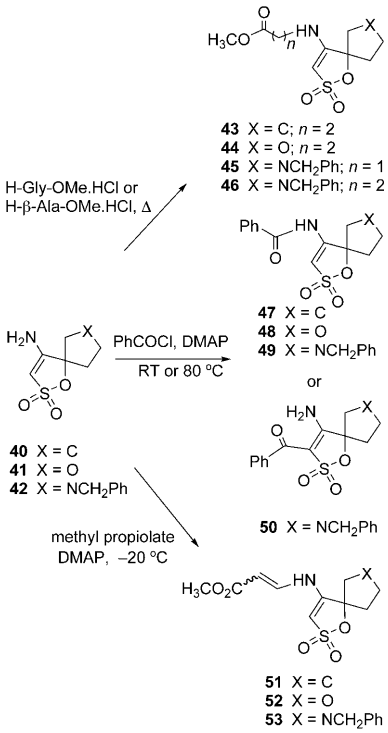
The marked reactivity difference found between the TSAO sultone system (in which the sultone moiety is fused to the C-3′ position of the ribose ring of TSAO nucleosides, Figure 1 below, Supporting Information) and the model substrates **5a**,**b** in the reactions with amines prompted us to investigate whether the spiranic (TSAO nucleosides) or non-spiranic nature of the model substrates **5a**,**b** could explain the experimental reactivity differences. Thus, the spiro-fused compounds **40**, **41** and **42** (Scheme 6) containing the β-amino-γ-sultone moiety were chosen as simple spiranic models and were subjected to transamination reactions. The synthesis of the simpler derivatives **40** and **41**, fused to a cyclopentane or a tetrahydrofuran ring, was carried out in a similar way to that described for the model substrates **5a**,**b**, starting from the appropriate commercially available cyclic ketone **34** and **35**,[22] by cyanohydrine formation, mesylation and base cyclisation. Thus, treatment of **34** and **35**[22] with trimethylsilyl cyanide in the presence of one equivalent of $BF_3{\cdot}Et_2O$ afforded the corresponding cyanohydrines, which were subsequently reacted with mesyl chloride in the presence of triethylamine as base to yield the desired alkyl sulfonate derivatives **37** and **38** (72 and 63% overall yield, respectively). Reaction of **37** and **38** with Cs_2CO_3 gave the desired fused spiro sultone derivatives **40** and **41** in good yields (91 and 70%, respectively). The spiro sultone compound **42** (Scheme 6) fused to a *N*-benzyl-3-pyrrolidine ring was similarly prepared by reaction of *N*-benzyl-3-pyrrolidinone (**36**) with potassium cyanide in water at 0°C, in the presence of sodium bicarbonate,[23] followed by mesylation (mesyl chloride/triethylamine) and base-cyclisation (Cs_2CO_3) to give the desired fused spiro derivative **42** in good yield.



Scheme 6.

Interestingly, reaction of spiro sultone derivatives **40**–**42** with an excess of amines such as glycine or β-alanine ester hydrochlorides in methanol under reflux, in a sealed tube for 24 h, afforded the *N*-alkyl derivatives **43**–**46** (Scheme 7) in moderate to good yields (40, 76, 67, and 62%, respectively). Thus, remarkable differences in the reactivity of the β-amino-γ-sultone heterocyclic system towards amines between spiranic and non-spiranic substrates were observed.

Theoretical studies, mentioned below, were carried out to rationalise these reactivity differences. As will be commented below, these studies further suggest that interaction of a tertiary amine, and consequently a base, on the C-4 position brings about an increase in the reactivity of spiranic substrates towards electrophiles. To test this prognosis, the reactivity of model spiranic β-amino-γ-sultone derivatives **40**–**42** towards electrophiles, such as benzoyl chloride or methyl propiolate, in the presence of DMAP as base, was next compared with that of model non-spiranic substrates **5a**,**b**. Interestingly, spiro sultone derivatives **40**–**42** reacted with benzoylchloride in the presence of DMAP in dry acetonitrile very rapidly and efficiently (Scheme 7). It took only 1–5 h at room temperature to go to completion, affording the *N*-benzoyl derivatives **47**–**49** in good yields (70, 71, and 78% yields, respectively). Thus, the rate of these *N*-benzoylations was dramatically increased in spiro sultone derivatives at room temperature (1–5 h for **40**–**42** compared with four days for compound **5b**). At higher temperature (80°C in a sealed tube) treatment of compound **42** with benzoylchloride and DMAP in dry acetonitrile gave the expected *C*-benzoyl derivative **50** in three hours in 67% yield. However, reaction of the simpler spiro sultone derivatives **40** and **41** under similar conditions with benzoylchloride and DMAP at 80°C led to product decomposition. Finally, reaction of compounds **40**–**42** with methyl propiolate and DMAP in acetonitrile at −20°C for 1–6 h gave a mixture of the *N*-alkylated derivatives of *E* and *Z* configuration **51**–**53** (Scheme 7) in higher yields than that of model non-spiranic substrates (45–57% yield for **40**–**42** vs. 17% yield for compounds **5a**,**b**). Therefore, the reactivity of the enaminic system of spiro sultone derivatives **40**–**42** towards benzoyl chloride, methyl propiolate or amines appears to be higher than that of non-spiranic substrates **5a**,**b**.

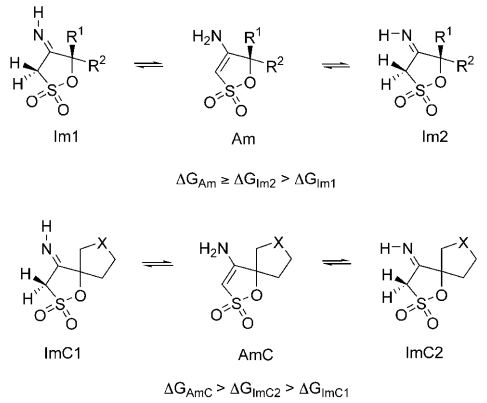


Scheme 7.

Theoretical study: A comparative computational study between spiranic and non-spiranic β-amino-γ-sultone sub-

strates was carried out in order to rationalise the experimental results described in this paper. All the β-amino-γ-sultone compounds (Am) together with their corresponding (*E*)- and (*Z*)-imine tautomers (Im) were modelled by means of DFT B3LYP/6-31G(d) calculations to determine the tautomer populations and their geometrical features.

The DFT quantum-mechanical calculations showed the relative Gibbs energy of the different tautomers to follow the order depicted in Scheme 8. The tendency in free energy indicates that the most stable isomer for all studied compounds is that of the amine. However, when the substituents on C-5 are not alicyclics, the imine tautomers have free energy values close to that found for the 4-amino one ($\Delta G_{Am} \geq \Delta G_{Im2} > \Delta G_{Im1}$).



Scheme 8. Gibbs energy orders for β-amino-γ-sultone tautomers.

In geometric terms, the differences between the diverse tautomers are important. Thus, the five-membered sultone cycle of the amine tautomer is almost flat, with the sulfur and carbon atoms C-3, C-4 and C-5 forming a plane, whereas the oxygen atom of the cycle forms a rough envelope conformation. This oxygen atom has a flap angle higher than 175° in relation to that plane. Regarding the imine conformations, the sultone ring forms a more real envelope conformation in which the flap atom is placed, in this case, on the sulfur atom (Figure 1). This conformational change, as commented below, seems to be responsible for the peculiar reactivity of these chemical systems towards several molecules. Also, the conformational divergence depends on the substituents at the C-5 position. Thus, when R^1 and R^2 are linear chains, the conformational change when the system goes from the amine tautomer to the imine ones is easily achieved. However, when R^1 and R^2 form an alicyclic moiety, this conformational change is more difficult to achieve, because both cycles, joined by a spiranic carbon, are mutually hindering, and an energetic and synergic agreement between both cycles has to be accomplished to permit successful proton transfer.

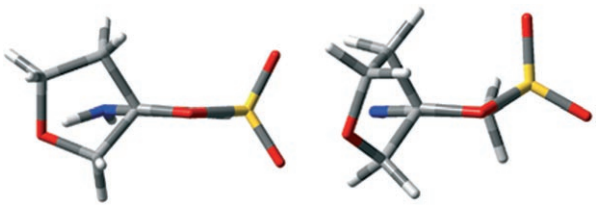


Figure 1. Molecular modelling, B3LYP/6–31G(d) geometry for 4-amino tautomer of **41** (left) and (*Z*)-imine tautomer of **41** (right).

On calculating the Mulliken and ESP charges by computational chemistry methods, it is observed that the β-amino-γ-sultone ring has two electron-rich atoms centred on the C-3 and 4-amino atoms (Figure 2). HOMO energy values,

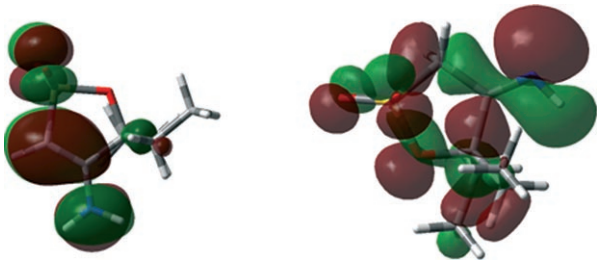
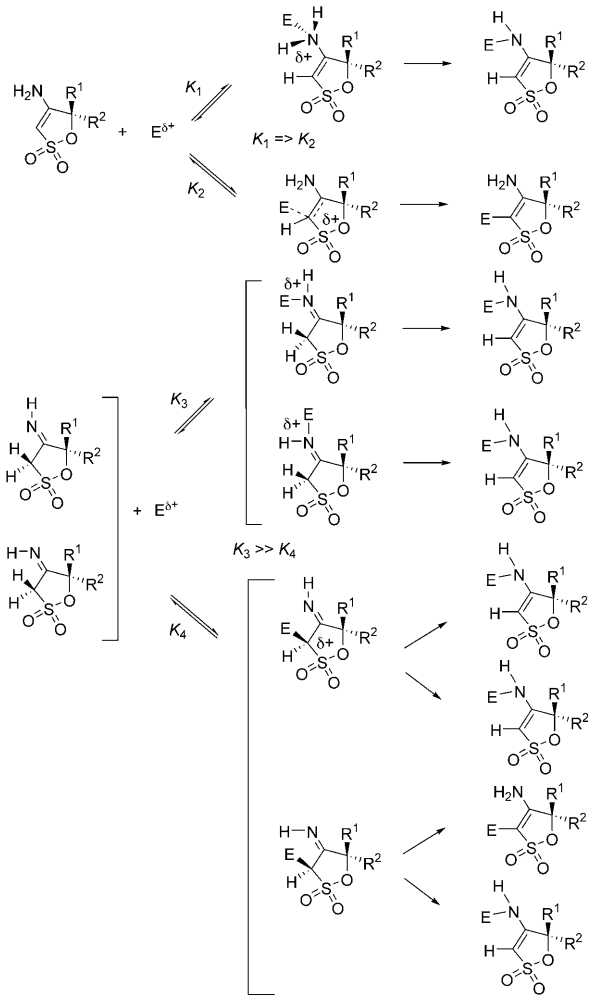


Figure 2. HOMO representation of amine tautomer (left) and (*Z*)-imine tautomer of **40** (right).

close to −6.5 eV for the 4-amino derivatives and near 7.0 eV for the (*Z*)- and (*E*)-imine tautomers, indicate that these molecules have a slightly hard behaviour and that the amine nitrogen atom is more nucleophilic than the imine ones. Also, the HOMO electron density for the amine tautomer is mainly centred on the C-3 and 4-amino atoms, with the higher electron density placed on C-3, no matter which compound is analyzed. For the imine compounds, the HOMO electron density, even though it is more delocalised, is mainly centred on the NH imine moiety having the C-3 atom with lower electron density than the nitrogen one. Therefore, the reactivity towards electrophiles will depend on the ratio of tautomers present in the reaction system. Thus, attending to electronic features, the 4-amino tautomers will react towards electrophiles both on the nitrogen and C-3 atoms, even though the product ratio should be slightly displaced to the reaction on N-4, whilst the (*E*)- or (*Z*)-imine tautomers will react mostly at the N-4 position.

In Scheme 9 the plausible reactions for β-amino-γ-sultone derivatives and their corresponding tautomers with electrophiles are shown. This scheme also depicts the relative equilibrium constants of the obtained product ratio. To justify the latter scheme derived from the analysis of the HOMO frontier orbital, quantum calculations were also carried out to model these electrophilic reactions on the C-3 and 4-amino positions. It could be observed that both positions are able to undergo electrophilic reactions. When an ethyl cation, chosen as an electrophilic probe for the sake of simplicity, was allowed to interact with the compound described in this paper, the intermediate state of the attack on the C-3 position had higher energy than that of the attack on the 4-



Scheme 9. Electrophilic reactions of β-amino-γ-sultone derivatives and their corresponding tautomers.

amino one (Scheme 9). However, the final state of the attack on the 4-amino position had the lowest free energy. Also, it was found by thermodynamic reasoning that the attack on the C-3 position of the imine moiety is reversible, resembling the tautomerism of the proton, and hence, instead of a proton making the interchange, the electrophile seems to be able to jump from the C-3 position to the 4-amino one. These calculations are thus capable of justifying the obtained experimental results. After the first electrophilic reaction, another one is possible on the other reactive position. In conclusion, both C-3 and 4-amino positions will be capable of undergoing electrophilic reactions, and the reaction products will depend on the substrate, the used electrophile (soft or hard) and the reaction conditions (pH, temperature, time, etc.).

Theoretical studies of β-amino-γ-sultone substrates towards nucleophiles were also performed. LUMO diagrams show the C-4 position to be the most favourable for attack by nucleophiles (Figure 3). Also, the lobes of the LUMO centred on the C-3 and 4-amino positions allow justification of the feasibility of these systems to undergo the proton

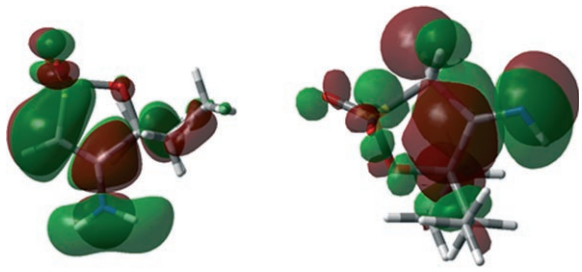
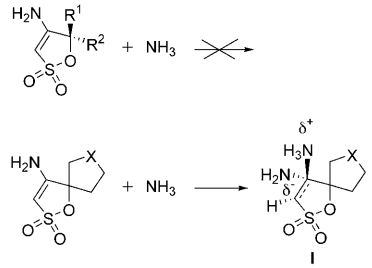


Figure 3. LUMO representation of amine tautomer (left) and (*Z*)-imine tautomer of **40** (right).

transpositions necessary to rationalise the interconversion between the amino and imine tautomers.

The dramatic difference in reactivity of spiranic versus non-spiranic sultone derivatives towards amines as nucleophiles cannot be explained by considering solely the frontier orbitals of these substrates and nucleophiles. Therefore, a computational study of the reactions by nucleophiles towards the 4-amino-1,2-oxathiole-2,2-dioxide heterocyclic systems was carried out. For the sake of simplicity, the transamination reactions were modelled by placing an ammonia molecule (as a simple amine probe) near the C-2 position. In this context, the ammonia nucleophile moiety was placed at 2.0 Å, calculating the optimised geometry for two models: one simulating the attack from the top, and the other from the bottom of the five-membered sultone ring plane.

As shown in Scheme 10, for the non-spiranic sultone compounds it was not possible to find any energy minimum or intermediate state for the reaction of NH_3 with the amino-derivative, because the nucleophile was ejected from the initial distance to distances larger than 3.5 Å, showing that this molecule is not able to interact with the C-4 carbon. However, NH_3 was able to interact in all the spiranic compounds, forming an intermediate compound (**I**) that was able to progress towards the transamination compound. The intermediate **I** is only produced when the ammonia molecule interacts with the C-4 position through one side (top position of Scheme 10). This intermediate state showed a contorted conformation on the sultone ring, which is not flat, showing an envelope conformation with the spiranic carbon being the flap atom (E^5). This state is stabilised because the other ring also undergoes a conformational change. Both coordi-



Scheme 10.

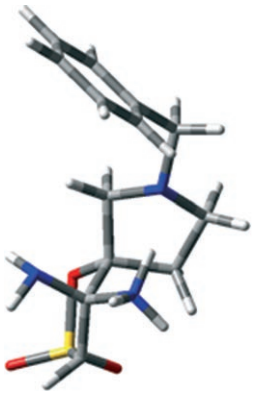


Figure 4. Molecular model of the resultant intermediate (**I**) of the reaction between **42** and NH_3.

nated changes are able to lessen the energy of the system, producing the intermediate compound (Figure 4). The lowest relative Gibbs energies for the intermediate compounds ($\Delta G^S = \Delta G^{intermediate} - \Delta G^{reactives} = \Delta G^{intermediate} - \Delta G^{sultone} - \Delta G_{NH_3}$) were found for the intermediates derived from **41** ($\Delta G^S = 50.32$ kcal mol^{-1}) and **42** ($\Delta G^S = 48.21$ kcal mol^{-1}), being slightly higher for **40** ($\Delta G^S = 57.32$ kcal mol^{-1}). The progress of the reaction is easily achieved by transfer of a proton from the NH_3 group to the NH_2 one, with release of the protonated group, NH_3. The stage resultant of the proton transfer matches with the attack on the non-reactive side, and hence the NH_3 is released, yielding the transamination product. Evidently, if the nucleophile is an amine (RNH_2), the resultant compound is the transamination product, in which the resultant moiety placed on C-4 is NHR.

Furthermore, the conformational change mentioned above, needed to produce the intermediate compound (**I**, Scheme 10), may bring about an increase of electron density on the N-4 and C-3 atoms. In particular, the HOMO graph (Figure 5) indicates that the highest electron density is located on the C-3 carbon. Also, the amine group attached to that carbon is out of the plane of the sultone envelope, its nature being more sp^3, and thus more reactive to electrophiles. As an example, the HOMO graph for the intermediate compound derived from **41** is portrayed in Figure 5.

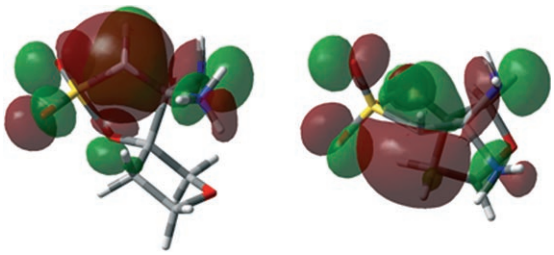


Figure 5. HOMO graph of the intermediate state **I** resultant of the reaction between **41** and NH_3.

This increase of electron density on the N-4 and C-3 atoms, on the intermediate state resulting from the interaction of a nucleophile on C-4, may anticipate an enhanced reactivity of spiranic substrates towards electrophiles in the presence of amines as bases, compared with the non-spiranic substrates. Thus, a similar computational study replacing the ammonia molecule by a tertiary amine as a base was carried out. In this case, NMe_3 was used as a simple probe and it was placed at 2.0 Å from the C-4 position. Again, similar intermediate states to those found above were obtained only for spiranic compounds. In this case, the lowest ΔG^S intermediate was that derived from **41** ($\Delta G^S = 65.91$ kcal mol^{-1}), whilst the highest one corresponded to **40** ($\Delta G^S = 89.23$ kcal mol^{-1}). As an example, the geometry conformation of the intermediate state derived from **41** is depicted in Figure 6. The obtained geometry is analogous to the geometry of the intermediate of the reaction with NH_3. However, the distances N(NH_3)···C4 were lower than N(NMe_3)···C4 for the intermediates resulting from the interaction with NMe_3. Thus, in absolute terms, the electronic interaction is lower than that obtained for the reaction with ammonia.

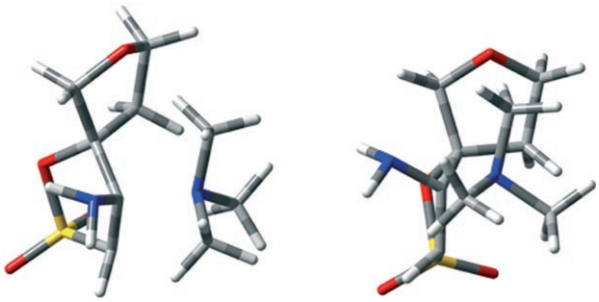
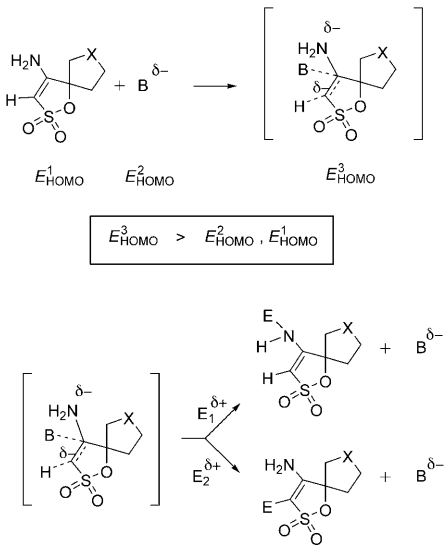


Figure 6. Geometry of the intermediate state resultant of the interaction between **41** and NMe_3.

Again, the electron density is mainly located on the C-3 and N-4 atoms. Thus, after the interaction of the nucleophile (NMe_3), the 4-amino group is geometrically out of plane with a structure like an aliphatic amine (sp^3) with enhanced reactivity and capable of reacting under mild conditions with electrophilic entities. Also, the C-3 position showed the HOMO highest density, and, therefore, may be able to react with the same electro-deficient systems. The enhancing of reactivity is evident from observation of the HOMO energy. The HOMO energy is −6.59 eV for **41**, −5.60 eV for NMe_3, and −5.05 eV for the intermediate compound. This lower E_{HOMO} of the intermediate compound means a higher reactivity towards electrophiles, which has been supported experimentally, as mentioned before. The reactivity of positions C-3 and N-4 will depend on the electrophile used and the reaction conditions. Paying attention to this result, the reactivity of these systems is explained and summarised in Scheme 11.

Conclusion

The reactivity of the readily available 4-amino-5*H*-1,2-oxathiole-2,2-dioxide (β-amino-γ-sultone) heterocyclic system toward electrophiles and amines has been studied. One of the interesting features of the system is its ambident nucleophilicity: nucleophilic reaction can take place at the site of the enaminic carbon atom (C-3) and/or the primary amino nitrogen atom, depending on the nature of the electrophile



Scheme 11. Geometrical and electronic (E_{HOMO}) parameters for the intermediate resulting from the reaction of spiranic compounds with electrophiles (E_1, E_2) in the presence of a base (top) along with its reaction products (bottom).

and the reaction conditions. On the other hand, amines react at the C-4 position of the heterocycle through an exchange with the amino function only in spiranic substrates bearing alicyclic substituents at the C-5 position. Theoretical studies indicate that the reactivity of spiranic systems towards amines is primarily controlled by conformational changes on intermediate compounds. Furthermore, the calculations predict an enhanced reactivity of spiranic substrates towards electrophiles in the presence of amines. This increase of reactivity on spiranic derivatives comes from the interaction of an electron-rich moiety, such as an amine at the C-4 position. This interaction brings about a conformational change with breaking of the planarity of the sultone ring, which increases the reactivity of the C-3 and N-4 positions towards electrophiles. This is supported by experimental results, which indicated that the rate or yields of the reaction of spiranic substrates with electrophiles, such as benzoyl chloride or methyl propiolate in the presence of a tertiary amine (DMAP), were dramatically increased when compared with model non-spiranic substrates. These studies represent a clear example of how an electronic interaction is able to induce conformational changes that lead to intermediate states with increase reactivity.

Experimental Section

Chemical procedures: Melting points were determined in a Reichert-Jung Thermovar hot-stage microscope equipped with a polarizer. IR spectra were obtained on a Perkin–Elmer Spectrum One spectrophotometer. Microanalyses were carried out on a CHN-O-RAPID instrument. Mass spectra were measured on a quadropole mass spectrometer equipped with an electrospray source (LC/MC HP 1100). ^{1}H NMR spectra were recorded with a spectrometer operating at 300, 400, and 500 MHz with Me_4Si as the internal standard. ^{13}C NMR spectra were recorded with a spectrometer operating at 75, 100, and 125 MHz. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254}. Separations on silica gel were performed by preparative centrifugal circular thin-layer chromatography (CCTLC) on a Chromatotron (Kiesegel 60 PF_{254} gipshaltig, layer thickness of 1 mm, flow rate of 5 mL min^{-1}). Flash column chromatography was performed with silica gel 60 (230–400 mesh). Liquid chromatography was performed using a force flow (flash chromatography) HPFC Horizon system with Flash 25 M cartridges (KP-Sil Silica, 60 Å, 40–63 μM).

Triethylamine, 1,4-dioxane, dichloromethane, 1,2-dichloroethane, acetonitrile, and ethanol were dried by heating under reflux over calcium hydride. Tetrahydrofuran was dried by heating under reflux over sodium/benzophenone.

2-Benzyl-2-hydroxy-3-phenylpropionitrile (2a)

Method A: $NaHCO_3$ (79 mg, 0.94 mmol) and sodium cyanide (24 mg, 0.48 mmol) were added to a solution of **1a** (100 mg, 0.48 mmol) in diethyl ether (2 mL)/water (1 mL). The mixture was stirred at room temperature for 40 h. The organic layer was separated and the aqueous phase was further extracted with diethyl ether (2×10 mL). The combined organic extracts were dried and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate 1:2), to give **2a** (45 mg, 40%) as a white amorphous solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 2.96 (s, 4H), 6.49 (br s, 1H), 7.42 ppm (m, 10H). The slowest moving band afforded 40 mg (40%) of unreacted starting material (**1a**).

Method B: Trimethylsilyl cyanide (130 μL, 0.96 mmol) and boron trifluoride diethyl etherate (12 μL, 0.096 mmol) were added to a solution of **1a** (100 mg, 0.48 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 0.5 h. The solvent was evaporated to dryness. A solution of 3 N HCl (5 mL) was added and the resulting suspension was stirred at room temperature for 12 h. Volatiles were removed and the residue, thus obtained, was dissolved in ethyl acetate (10 mL) and washed, successively, with aqueous $NaHCO_3$ (2×5 mL) and brine (2×5 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2) to give **2a** (80 mg, 70%) as a white foam.

Method C: Trimethylsilyl cyanide (400 μL, 3 mmol) and boron trifluoride diethyl etherate (253 μL, 2 mmol) were added to solution of **1a** (420 mg, 2 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 2 h and the solvent was evaporated to dryness. The residue, thus obtained, was dissolved in ethyl acetate (10 mL), washed with brine (2×5 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2) to give **2a** (430 mg, 90%) as a white foam.

2-Benzyl-2-(methanesulfonyloxy)-3-phenylpropionitrile (4a): Et_3N (1.9 mL, 14 mmol) was added to a solution of **2a** (600 mg, 2.2 mmol) in dry dichloromethane (5 mL). The mixture was cooled to −30 °C and methanesulfonyl chloride (460 μL, 6 mmol) was slowly added. The mixture was stirred at −20 °C for 1 h and at 0 °C for an additional hour. Volatiles were removed and the residue was dissolved in ethyl acetate (10 mL) and washed successively with water (10 mL) and brine (2× 10 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by flash column chromatography on silica gel (hexane: ethyl acetate, 10:1) to give **4a** (0.55 g, 80%) as a white amorphous solid. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ = 2.85 (s, 3H), 3.42 and 3.47 (AB system, J = 9.4 Hz, 4H), 7.38 ppm (m, 10H); IR (film): $\tilde{\nu}$ = 2541 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{17}NO_3S$: C 64.74, H 5.43, N 4.44, S 10.17; found: C 64.44, H 5.09, N 4.67, S 9.98. The slowest moving band afforded 30 mg (5%) of unreacted starting material (**2a**).

4-Amino-5,5-dibenzyl-5*H*-1,2-oxathiole-2,2-dioxide (5a): Caesium carbonate (490 mg, 1.5 mmol) was added to a suspension of **4a** (310 mg, 1 mmol) in dry acetonitrile (3 mL), and the mixture was stirred at room temperature for 2 h. Solvent was removed and the residue, thus obtained, was dissolved in ethyl acetate (20 mL) and washed successively with water (10 mL) and brine (2×10 mL). The organic phase was dried (Na_2SO_4) and filtered, followed by evaporation of the solvent. The residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 3:1) to give **5a** (270 mg, 80%) as a white solid. M.p. (toluene): 225–

226 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta = 3.12$ and 3.35 (AB system, $J = 14.5$ Hz, 4H), 5.21 (s, 1H), 6.33 (brs, 2H, NH_2), 7.30 ppm (m, 10H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 43.4$, 90.1, 92.2, 128.2, 129.1, 132.1, 135.9, 142.5, 158.5 ppm; IR (film): $\tilde{\nu} = 3501$, 3407 cm^{-1}; MS (ES$^+$): m/z: 316.1 $[M+1]^+$, 338.1 $[M+Na]^+$, 631.2 $[2M+1]^+$, 653.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{17}NO_3S$: C 64.74, H 5.43, N 4.44, S 10.17; found: C 64.50, H 5.03, N 4.12, S 10.03.

4-Benzylamino-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide, 4-amino-3,5-dibenzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide and 4-benzylamino-3,5-dibenzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (7, 8 and 9a): A solution of **5b** (100 mg, 0.40 mmol) and NaH (21 mg, 0.88 mmol) in dry THF (5 mL) was stirred at room temperature for 10 min. Then, benzylbromide (147 μL, 0.99 mmol) was added and the mixture was stirred at room temperature for 19 h and neutralised with acetic acid to pH ≈ 7. The residue obtained after evaporation was purified by HPFC on a Horizon system (hexane/ethyl acetate, 2:1). From the fastest moving band **9a** (25 mg, 15%) was isolated as a white amorphous solid. M.p. (hexane/ethyl acetate): 187–188 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta = 1.03$ (t, $J = 7.0$ Hz, 3H), 1.91 (m, 1H), 2.18 (m, 1H), 3.35 (s, 2H), 3.55 and 3.63 (AB system, $J = 18.3$ Hz, 2H), 4.24 (ABX system, $J = 5.9$ and 15.6 Hz, 1H), 4.25 (ABX system, $J = 7.4$ and 15.6 Hz, 1H), 6.42 (ABX system, $J = 5.9$ and 7.4 Hz), 1H, 6.98 (d, $J = 7.3$ Hz, 2H), 7.16 (t, $J = 7.3$ Hz, 1H), 7.22 (t, $J = 7.3$ Hz, 2H), 7.33 ppm (m, 10H); ^{13}C NMR [125 MHz, $(CD_3)_2CO$] $\delta = 7.9$, 28.4, 30.7, 44.3, 47.6, 92.2, 97.9, 126.9, 127.3, 127.8, 128.2, 128.4, 128.8, 129.2, 129.5, 131.9, 135.5, 140.4, 140.5, 151.4 ppm; MS (ES$^+$): m/z: 434.3 $[M+1]^+$, 451.3 $[M+H_2O]^+$, 889.3 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{27}NO_3S$: C 72.03, H 6.28, N 3.23, S 7.40; found: C 71.89, H 5.99, N 3.00, S 7.12.

The next moving band gave 28 mg (21%) of **7** as a white foam. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 0.87$ (t, $J = 7.2$ Hz, 3H), 1.74 (m, 1H), 2.03 (m, 1H), 3.25 (s, 2H), 4.31 (d, $J = 5.5$ Hz, 2H), 5.40 (s, 1H), 6.69 (brt, $J = 5.5$ Hz, 1H; NH), 7.35 ppm (m, 10H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 6.8$, 28.9, 44.1, 48.9, 87.6, 92.1, 127.1, 127.8, 128.1, 128.8, 131.1, 134.9, 137.5, 157.1 ppm; MS (ES$^+$): m/z: 344.3 $[M+1]^+$, 366.3 $[M+Na]^+$, 709.1 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{21}NO_3S$: C 66.45, H 6.16, N 4.08, S 9.34; found: C 66.23, H 5.99, N 3.89, S 8.97.

The slowest moving band afforded 13 mg (10%) of **8** as a white foam. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta = 0.93$ (t, $J = 7.5$ Hz, 3H), 1.82 (m, 1H), 2.08 (m, 1H), 3.25 (s, 2H), 3.58 and 3.63 (AB system, $J = 17.3$ Hz, 2H), 5.83 (brs, 2H; NH_2), 7.16 (d, $J = 7.3$ Hz, 2H), 7.19 (m, 1H), 7.20 (m, 2H), 7.30 ppm (m, 5H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): $\delta = 14.4$, 27.6, 44.3, 92.0, 100.1, 126.9, 127.7, 128.7, 128.9, 129.0, 131.8, 135.5, 138.3, 152.3 ppm; MS (ES$^+$): m/z: 344.3 $[M+1]^+$, 361.2 $[M+H_2O]^+$, 366.2 $[M+Na]^+$, 709.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{21}NO_3S$: C 66.45, H 6.16, N 4.08, S 9.34; found: C 66.32, H 6.01, N 3.87, S 9.31.

5,5-Dibenzyl-3-methyl-4-methylamino-5*H*-1,2-oxathiole-2,2-dioxide (9b): A solution of **5a** (100 mg, 0.32 mmol) and KOH (54 mg, 0.90 mmol) in dry 1,4-dioxane (15 mL) was stirred at room temperature for 15 min. Then MeI (126 μL, 0.90 mmol) was added. The mixture was stirred at room temperature for 24 h, neutralised with acetic acid and concentrated to dryness. The residue was treated with ethyl acetate (2×5 mL) and brine (5 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:1) to give **9b** (30 mg, 27%) as a white amorphous solid. M.p. (hexane/ethyl acetate): 213–214 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 1.90$ (s, 3H), 3.03 (d, $J = 5.1$ Hz, 3H), 3.05 and 3.26 (AB system, $J = 14.5$ Hz, 4H), 6.81 (br s, 1H; NH), 7.25 ppm (m, 10H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 7.1$, 29.8, 41.9, 88.9, 126.1, 126.3, 130.0, 134.4, 142.1 ppm; MS (ES$^+$): m/z: 344.2 $[M+1]^+$, 366.6 $[M+Na]^+$, 711.3 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{21}NO_3S$: C 66.45, H 6.16, N 4.08, S 9.34; found: C 66.21, H 6.01, N 3.87, S 9.11.

5,5-Dibenzyl-4-[(dimethylamino)methylen]amino-5*H*-1,2-oxathiole-2,2-dioxide (10a): *N,N*-Dimethylformamide dimethyl acetal (170 μL, 1.28 mmol) was added to a solution of **5a** (100 mg, 0.32 mmol) in dry DMF (10 mL). The reaction mixture was stirred at 40 °C for 40 min. The solvent was evaporated to dryness and the residue was purified by HPFC on an Horizon system (hexane/ethyl acetate 1:1) to give **10a** (115 mg, 97%) as a white solid. M.p. (dichloromethane/hexane): 181–182 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 3.05$ and 3.22 (AB system, $J = 13.5$ Hz, 4H), 3.18 (s, 6H), 5.76 (s, 1H), 7.25 (m, 10H), 7.88 ppm (s, 1H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta = 35.3$, 41.2, 43.4, 95.0, 98.5, 127.9, 128.9, 132.2, 136.5, 159.0, 165.7 ppm; MS (ES$^+$): m/z: 371.3 $[M+1]^+$; elemental analysis calcd (%) for $C_{20}H_{22}N_2O_3S$: C 64.84, H 5.99, N 7.56, S 8.66; found: C 64.56, H 5.62, N 7.33, S 8.28.

Reaction of sultone 5b with methyl propiolate

*5-Benzyl-5-ethyl-4-[(E)-2-(methoxycarbonyl)vinyl]amino-5H-1,2-oxathiole-2,2-dioxide ((E)-**12**) and (Z)-**12***: A solution of **5b** (100 mg, 0.39 mmol), methyl propiolate (42 μL, 0.47 mmol) and DMAP (57 mg, 0.47 mmol) in dry acetonitrile (10 mL) was stirred at 0 °C for 2 h. The solvent was removed and ethyl acetate was added (5 mL) and the mixture was washed with 0.1 N HCl (2×5 mL) and brine (2×5 mL). The organic layer was dried, filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2) to give a 90:10 mixture (20 mg, 17%) of (*E*)-**12** and (*Z*)-**12** as a white foam.

*Data for (E)-**12***: ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 0.90$ (t, $J = 7.5$ Hz, 3H), 1.85 (m, 1H), 2.03 (m, 1H), 3.25 (s, 2H), 3.65 (s, 3H), 5.52 (d, $J = 13.4$ Hz, 1H), 6.54 (s, 1H), 7.25 (m, 5H), 7.55 (dd, $J = 11.2$, 13.4 Hz, 1H), 8.87 ppm (d, $J = 11.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 23.3$, 28.9, 44.7, 51.8, 92.4, 95.9, 102.2, 127.8, 128.1, 128.5, 128.7, 130.9, 133.0, 139.7, 151.4, 167.0 ppm; IR (film): $\tilde{\nu} = 3405$, 1716 cm^{-1}; MS (ES$^+$): m/z: 338.0 $[M+1]^+$, 360.0 $[M+Na]^+$, 697.0 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{16}H_{19}NO_5S$: C 56.96, H 5.68, N 4.15, S 9.50; found: C 56.67, H 5.31, N 4.01, S 9.42.

*Data for (Z)-**12***: ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 3.78$ (s, 3H), 5.23 (d, $J = 6.3$ Hz, 1H), 6.41 ppm (s, 1H). The slowest moving band afforded 42 mg (42%) of unreacted starting material (**5b**).

*5-Benzyl-5-ethyl-4-propioloylamino-5H-1,2-oxathiole-2,2-dioxide (**14**)*: A solution of **5b** (100 mg, 0.39 mmol) and NaH 60% dispersion in mineral oil (32 mg, 0.78 mmol) in dry THF (5 mL) was stirred at room temperature for 1 h. Methyl propiolate (69 μL, 0.78 mmol) was added and the mixture was stirred at room temperature for 3 h. Solvent was removed and the residue was dissolved in ethyl acetate (5 mL) and the mixture was washed with water (2×5 mL) and brine (2×5 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 4:1) to give **14** (48 mg, 40%) as a white solid. M.p. (hexane/ethyl acetate): 136–137 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta = 0.87$ (t, $J = 7.3$ Hz, 3H), 1.85 (m, 1H), 2.17 (m, 1H), 3.28 and 3.36 (AB system, $J = 14.5$ Hz, 2H), 4.06 (s, 1H), 7.22 (s, 1H), 7.27 (m, 5H), 10.20 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 7.0$, 28.8, 43.5, 76.7, 79.0, 93.8, 107.0, 127.7, 128.6, 131.3, 134.4, 146.0, 151.0 ppm; IR (film): $\tilde{\nu} = 3508$, 2305, 1707 cm^{-1}; MS (ES$^+$): m/z: 306.0 $[M+1]^+$, 633.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{15}H_{15}NO_4S$: C 59.00, H 4.95, N 4.59, S 10.50; found: C 58.83, H 5.00, N 4.37, S 10.11.

Reaction of sultone 5b with acrylonitrile

Method A (2 equivalents of acrylonitrile and NaH): A solution of sultone **5b** (100 mg, 0.39 mmol) and NaH 60% dispersion in mineral oil (32 mg, 0.78 mmol) in dry THF (4 mL) was stirred at room temperature for 15 min. Acrylonitrile (52 μL, 0.78 mmol) was added and the mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (5 mL). The mixture was washed with water (2×10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by flash chromatography on silica gel (pentane/ethyl acetate, 1:1). From the fastest moving band, 5-benzyl-3-(2-cyanoethyl)-4-*bis*-(2-cyanoethyl)amino-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**15**) (35 mg, 25%) was isolated as a white foam. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta = 1.10$ (t, $J = 7.2$ Hz, 3H), 1.92 (ddd, $J = 5.2$, 11.2, 14.8 Hz, 1H), 2.15 (m, 1H), 2.20–2.51 (m, 5H), 2.54–2.66 (m, 1H), 2.82 (m, 2H), 3.04 (t, $J = 6.4$ Hz, 2H), 3.44 and 3.48 (AB system, $J = 15.2$ Hz, 2H), 4.17 (td, $J = 6.4$, 14.8 Hz, 1H), 4.36 (td, $J = 6.4$, 15.2 Hz, 1H), 7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 8.2$, 12.0, 12.3, 20.3, 26.7, 28.7, 40.5, 48.6, 65.8, 96.3, 119.3, 119.4, 119.8, 129.2, 129.6, 131.7, 134.9, 168.5 ppm; MS (ES$^+$): m/z: 435.2 $[M+Na]^+$, 413.3 $[M+1]^+$; elemental

analysis calcd (%) for $C_{21}H_{24}N_4O_3S$: C 61.14, H 5.86, N 13.58, S 7.77; found: C 61.08, H 5.79, N 13.72, S 7.58.

The slowest moving band afforded 5-benzyl-3-(2-cyanoethyl)-4-(2-cyanoethyl)amino-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**16**) (15 mg, 15%) as a white foam. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta=0.92$ (t, $J=7.6$ Hz, 3H), 1.78 (m, 1H), 2.09 (m, 2H), 2.57–2.72 (m, 2H), 2.89 (m, 3H), 3.26 (s, 2H), 3.85 (q, $J=6.4$ Hz, 2H), 6.19 (brt, $J=5.6$ Hz, 1H), 7.30 ppm (m, 5H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=7.5$, 18.2, 19.0, 20.1, 29.8, 41.0, 44.9, 92.4, 98.4, 118.9, 119.7, 127.9, 128.9, 131.9, 135.3, 150.2 ppm; MS (ES$^+$): *m/z*: 382.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{21}N_3O_3S$: C 60.15, H 5.89, N 11.69, S 8.92; found: C 60.21, H 5.96, N 11.75, S 9.14.

Method B (1 equivalent of acrylonitrile and NaH): A solution of sultone **5b** (100 mg, 0.39 mmol) and NaH 60% dispersion in mineral oil (16 mg, 0.39 mmol) in dry THF (4 mL) was stirred at room temperature for 15 min. Acrylonitrile (26 μL, 0.39 mmol) was added and the mixture was stirred at room temperature overnight. Solvent was removed and the residue was dissolved in ethyl acetate (10 mL) and the mixture was washed with water (2×10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by flash chromatography on silica gel (pentane/ethyl acetate, 1:1) From the slowest moving band a 2:1 mixture of 5-benzyl-3-(2-cyanoethyl)-4-(2-cyanoethyl)amino-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**16**) and 5-benzyl-4-(2-cyanoethyl)amino-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**17**) (49 mg, 41%) was obtained as a white foam. Compound **17**: ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta=0.85$ (t, $J=7.3$ Hz, 3H), 1.78 (m, 1H), 2.15 (m, 1H), 2.86 (m, 2H), 3.26 (s, 2H), 3.85 (q, $J=6.5$ Hz, 2H), 5.63 (s, 1H), 6.16 (brt, 6.4 Hz, 1H), 7.25–7.34 ppm (m, 5H); MS (ES$^+$): *m/z*: 307.5 $[M+1]^+$.

The fastest moving band afforded 49 mg (40%) of 4-amino-5-benzyl-3-(2-cyanoethyl)-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (**18**) as a white foam. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=0.91$ (t, $J=7.2$ Hz, 3H), 1.69–1.85 (m, 1H), 1.97–2.11 (m, 1H), 2.51–2.57 (m, 2H), 2.69–2.75 (m, 2H), 3.24 (s, 2H), 6.21 (bs, 2H) 7.26–7.32 ppm (m, 5H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=8.5$, 17.6, 19.9, 30.4, 45.6, 93.3, 99.3, 120.7, 128.8, 129.7, 132.8, 136.4, 154.0 ppm; MS (ES$^+$): *m/z*: 307.2 $[M+1]^+$; elemental analysis calcd (%) for $C_{15}H_{18}N_2O_3S$: C 58.80, H 5.92, N 9.14, S 10.47; found: C 58.95, H 5.94, N 9.35, S 10.53.

5,5-Dibenzyl-4-ureido-5*H*-1,2-oxathiole-2,2-dioxide (19): Chlorosulfonyl isocyanate (111 μL, 1.28 mmol) was added to a cooled (−30°C) solution of **5a** (100 mg, 0.32 mmol) in dry dichloromethane (5 mL), previously degassed under an argon atmosphere. The resulting mixture was stirred at −30°C for 20 min. Then, the reaction was quenched ($NaHCO_3$) and the organic layer was separated. The aqueous layer was extracted several times with ethyl acetate (3×10 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by CCTLC on the Chromatotron (ethyl acetate/methanol, 6:1) yielding 54 mg (46%) of compound **19** as a white solid. M.p. (toluene): 147–148°C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=3.10$ and 3.24 (AB system, $J=13.8$ Hz, 4H), 6.04 (brs, 2H; NH_2), 6.66 (s, 1H), 7.23 (m, 10H), 8.71 ppm (brs, 1H; NH); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta=43.8$, 92.3, 100.8, 128.2, 129.4, 131.9, 135.4, 149.5, 155.0 ppm; IR (film): $\tilde{\nu}=3687$, 3504, 1772 cm^{-1}; MS (ES$^+$): *m/z*: 359.1 $[M+1]^+$, 376.1 $[M+H_2O]^+$, 381.1 $[M+Na]^+$, 717.2 $[2M+1]^+$, 739.1 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{18}N_2O_4S$: C 60.32, H 5.06, N 7.82, S. 8.95; found: C 60.00, H 4.91, N 7.55, S 8.77.

5,5-Dibenzyl-4-ethoxycarbonylureido-5*H*-1,2-oxathiole-2,2-dioxide (20): Ethoxycarbonyl isocyanate (99 μL, 0.96 mmol) was added to a solution of **5a** (100 mg, 0.32 mmol) in dry acetonitrile (6 mL). The reaction mixture was stirred in an Ace pressure tube for 2.5 h at 100°C. Solvent was removed to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 2:1) to give **20** (127 mg, 93%) as a white solid. M.p. (hexane/ethyl acetate): 193–194°C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta=1.34$ (t, $J=7.3$ Hz, 3H), 3.28 (s, 4H), 4.35 (q, $J=7.3$ Hz, 2H), 6.83 (s, 1H), 7.28 (m, 10H), 9.88 (brs, 1H; NH), 10.46 ppm (brs, 1H; NH). ^{13}C NMR (125 MHz, $(CD_3)_2CO$): $\delta=13.9$, 42.9, 63.3, 91.5, 104.0, 127.6, 128.5, 131.0, 133.7, 146.3, 149.8, 155.7 ppm; IR (film): $\tilde{\nu}=$ 3399, 3222, 1744 cm^{-1}; MS (ES$^+$): *m/z*: 431.0 $[M+1]^+$, 453.0 $[M+Na]^+$, 882.9 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{21}H_{22}N_2O_6S$: C 58.59, H 5.15, N 6.51, S 7.45; found: C 58.33, H 4.91, N 6.33, S 7.39.

4-Benzoylamino-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (23): Benzoyl chloride (140 μL, 1.20 mmol) was added to a solution of **5a** (100 mg, 0.40 mmol) and DMAP (217 mg, 1.78 mmol) in dry acetonitrile (5 mL). The mixture was stirred at room temperature for 4 days. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2×5 mL) and brine (2×5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 5:1) to yield 100 mg (71%) of **23** as a white foam. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta=0.93$ (t, $J=7.2$ Hz, 3H), 1.86–1.96 (m, 1H), 2.30–2.39 (m, 1H), 3.40 and 3.47 (AB system, $J=14.4$ Hz, 2H), 7.25–7.33 (m, 2H), 7.45–7.66 (m, 4H), 7.61–7.67 (m, 2H), 7.86–7.89 (m, 1H), 8.03–8.05 (m, 2H), 9.58 ppm (brs, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=$ 8.5, 30.0, 44.9, 95.4, 106.8, 129.0, 129.9, 130.0, 131.4, 132.4, 132.7, 134.6, 134.7, 135.5, 136.0, 148.6, 168.6 ppm; MS (ES$^+$): *m/z*: 358.3 $[M+1]^+$; elemental analysis calcd (%) for $C_{19}H_{19}NO_4S$: C 63.85, H 5.36, N 3.92, S 8.97; found: C 63.91, H 5.41, N 4.09, S 9.06.

4-Amino-3-benzoyl-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (24): Benzoyl chloride (140 μL, 1.20 mmol) was added to a solution of **5b** (100 mg, 0.39 mmol) and DMAP (217 mg, 1.78 mmol) in dry acetonitrile (5 mL). The mixture was stirred in an Ace pressure tube for 3 h at 80°C. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2× 5 mL) and brine (2×5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 25:1) to yield 97 mg (69%) of **24** as a white amorphous solid. M.p. (hexane/ethyl acetate): 201–202°C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=0.97$ (t, $J=7.5$ Hz, 3H), 1.88 (m, 1H), 2.24 (m, 1H), 3.33 and 3.43 (AB system, $J=14.2$ Hz, 2H), 7.23–7.90 (m, 10H), 8.25 (brs, 1H; NH), 9.51 ppm (brs, 1H; NH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): $\delta=7.9$, 29.5, 44.8, 91.6, 105.5, 128.5, 128.8, 129.4 132.2, 132.9, 135.2, 140.4, 169.5, 188.5 ppm; IR (film): $\tilde{\nu}=3462$, 1630 cm^{-1}; MS (ES$^+$): *m/z*: 358.1 $[M+1]^+$, 375.2 $[M+H_2O]^+$, 380.0 $[M+Na]^+$, 737.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{19}NO_4S$: C 63.85, H 5.36, N 3.92, S 8.97; found: C 63.69, H 5.25, N 3.88, S 9.12.

4-Amino-5-benzyl-5-ethyl-3-(α-hydroxybenzyl)-5*H*-1,2-oxathiole-2,2-dioxide (25): A solution of **5b** (100 mg, 0.39 mmol) in dry THF (5 mL), previously degassed under an argon atmosphere, was reacted with NaH 60% dispersion in mineral oil (32 mg, 0.78 mmol) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to −78°C, benzaldehyde (79 μL, 0.78 mmol) was added and the mixture was stirred for 10 min. After quenching the reaction with water (2 mL), the solvent was evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 2:1). The faster moving band afforded **25** (15 mg, 10%) as an amorphous solid. M.p. (hexane/ethyl acetate): 141–143°C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=$ 0.78 (t, $J=7.2$ Hz, 3H), 1.64 (m, 1H), 1.95 (m, 1H), 3.23 (s, 2H), 5.19 (brs, 1H), 5.62 (s, 1H), 5.81 (brs, 2H), 7.29 (m, 8H), 7.52 ppm (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=7.1$, 28.6, 44.1, 67.1, 90.8, 103.1, 126.8, 127.4, 127.7, 128.4, 128.5, 131.5, 135.3, 142.5, 153.1 ppm; IR (film): $\tilde{\nu}=3583$, 3497, 3395 cm^{-1}; MS (ES$^+$): *m/z*: 382.0 $[M+Na]^+$, 741.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{21}NO_4S$: C 63.49, H 5.89, N 3.90, S 8.92; found: C 63.32, H 5.71, N 3.72, S 8.67.

4-Amino-3-benzoyl-5,5-dibenzyl-5*H*-1,2-oxathiole-2,2-dioxide (26): A solution of **5a** (100 mg, 0.32 mmol), in dry THF (5 mL) under argon, was reacted with NaH 60% dispersion in mineral oil (26 mg, 0.64 mmol) at room temperature for 10 min. Then, benzaldehyde (65 μL, 0.64 mmol) was added and the mixture was refluxed for 10 min. After quenching the reaction with methanol (2 mL), the solution was stirred at room temperature for 5 min. The solvent was evaporated and the residue was dissolved in ethyl acetate (5 mL). The organic layer was successively washed with 1N HCl (2×5 mL) and brine (2×5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 10:1) to give **26** (118 mg, 88%) as a white amorphous solid. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta=3.27$ and

3.55 (AB system, $J=14.5$ Hz, 4H), 7.34 (m, 12H), 7.52 (m, 1H), 7.74 (m, 2H), 8.20 (brs, 1H; NH), 9.21 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=42.8$, 89.7, 105.5, 127.8, 128.0, 128.6, 128.7, 131.5, 132.2, 134.3, 139.5, 168.3, 187.5 ppm; MS (ES^+): m/z: 420.1 $[M+1]^+$, 437.1 $[M+H_2O]^+$, 861.1 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{24}H_{21}NO_4S$: C 68.72, H 5.05, N 3.34, S 7.64; found: C 68.39, H 4.91, N 3.11, S 7.22.

4-Amino-5,5-dibenzyl-3-iodo-5*H*-1,2-oxathiole-2,2-dioxide (29): A 5% solution of iodine in ethanol was added dropwise to a solution of **5a** (100 mg, 0.32 mmol) and $NaHCO_3$ (267 mg, 3.2 mmol) in dry ethanol (10 mL), until the colour of the reaction mixture remained light brown. Then, solvent was evaporated and the residue was treated with cold (4°C) ethyl acetate (30 mL), cold (4°C) brine (15 mL) and cold (4°C) 5% aqueous $NaHSO_3$ solution (7 mL). The organic layer was separated and the aqueous layer was extracted with cold (4°C) ethyl acetate (3× 10 mL). The combined organics were washed with brine (3×5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:1) to give **29** (99 mg, 70%) as a white solid. M.p. (toluene): 223–224°C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=3.16$ and 3.38 (AB system, $J=14.3$ Hz, 4H), 6.49 (brs, 2H), 7.25 ppm (m, 10H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=$ 43.1, 44.0, 93.8, 127.9, 128.8, 131.6, 134.9, 158.6 ppm; MS (ES^+): m/z: 442.1 $[M+1]^+$, 904.9 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{16}INO_3S$: C 46.27, H 3.65, N 3.17, S 7.27; found: C 46.00, H 3.54, N 3.01, S 6.98.

4-Amino-5,5-dibenzyl-3-nitroso-5*H*-1,2-oxathiole-2,2-dioxide (31a): Sodium nitrite (44 mg, 0.64 mmol) was slowly added over 30 min to a solution of **5a** (100 mg, 0.32 mmol) in acetic acid (8 mL)/water (0.8 mL)/ methanol (1 mL) at 10°C. The reaction mixture was stirred at 10°C for 4 h and the solvent was removed. The residue was neutralised with a saturated aqueous solution of $NaHCO_3$ to pH≈7, and it was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 6:1) to give **31a** (89 mg, 81%) as a blue solid. M.p. (dichloromethane/hexane): 198–199°C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta=3.30$ and 3.61 (AB system, $J=14.5$ Hz, 4H), 7.31 ppm (m, 10H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$): $\delta=42.1$, 88.5, 88.7, 127.2, 127.9, 130.5, 130.7, 132.7, 132.8, 168.4 ppm. IR (film): $\tilde{\nu}=3484$, 3407, 1653 cm^{-1}; MS (ES^+): m/z: 345.0 $[M+1]^+$; elemental analysis calcd (%) for $C_{17}H_{16}N_2O_4S$: C 59.29, H 4.68, N 8.13, S 9.31; found: C 59.01, H 4.60, N 7.89, S 9.00.

5,5-Dibenzyl-4-oxo-1,2-oxathiolane-2,2-dioxide (32a): A solution of **5a** (100 mg, 0.32 mmol) in 1N HCl in methanol (17 mL) was stirred at room temperature for 14 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate. The mixture was washed with water (10 mL), brine (10 mL), and $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 10:1) to give **32a** (85 mg, 85%) as a white solid. M.p. (ethanol/water): 78–79°C; Tautomer **A**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.02$ and 3.23 (AB system, $J=14.2$ Hz, 4H), 3.03 (s, 2H), 7.17 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=41.5$, 53.8, 100.2, 127.9, 128.7, 130.8, 132.7, 200.6 ppm; IR (film): $\tilde{\nu}=1764$, 1369 cm^{-1}; Tautomer **B**: ^{1}H NMR (400 MHz, $(CD_3)_2SO$): $\delta=3.02$ and 3.17 (AB system, $J=13.9$ Hz, 4H), 5.86 (s, 1H), 7.27 (m, 10H), 12.84 ppm (brs, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): $\delta=41.4$, 91.8, 94.8, 127.0, 128.0, 130.7, 134.1, 166.2 ppm; MS (ES^+): m/z: 317.0 $[M+1]^+$, 334.0 $[M+H_2O]^+$, 339.0 $[M+Na]^+$, 655.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{16}O_4S$: C 64.54, H 5.10, S 10.14; found: C 64.32, H 4.87, S 9.87.

4-Methoxycarbonylethylamino-1-oxa-2-thiaspiro[4.4]non-3-ene-2,2-dioxide (43): A solution of **40** (100 mg, 0.53 mmol) and H-β-Ala-OMe·HCl (221 mg, 1.59 mmol) in methanol (5 mL) was stirred in an Ace pressure tube for 24 h at 100°C. The solvent was evaporated and the residue was purified by HPFC on a Horizon system (dichloromethane/methanol, 200:1) to give **43** (58 mg, 40%) as a white solid. M.p. (hexane/ethyl acetate): 98–99°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.79$–1.99 (m, 6H), 2.18 (m, 2H), 2.63 (t, $J=6.3$ Hz, 2H), 3.33 (q, $J=6.3$ Hz, 2H), 3.72 (s, 3H), 4.84 (brt, $J=6.3$ Hz, 1H), 5.27 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=25.1$, 32.5, 38.2, 38.6, 41.1, 52.5, 86.8, 97.2, 157.9, 172.9 ppm. IR (film): $\tilde{\nu}=3429$, 1733 cm^{-1}; MS (ES^+): m/z: 276.0 $[M+1]^+$, 573.3 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{17}NO_5S$: C 47.99, H 6.22, N 5.09, S 11.65; found: C 48.03, H 6.18, N 5.19, S 11.59.

4-Amino-3-benzoyl-1-oxa-2-thiaspiro[4.4]non-3-ene-2,2-dioxide (47): Benzoyl chloride (124 μL, 1.08 mmol) was added to a solution of **40** (100 mg, 0.36 mmol) and DMAP (176 mg, 1.44 mmol) in dry acetonitrile (5 mL). The mixture was stirred at room temperature for 5 h. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2×5 mL) and brine (2×5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 3:1) to yield 108 mg (70%) of **47** as a white foam. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=1.87$–203 (m, 6H), 2.35 (m, 2H), 7.35 (s, 1H), 7.45 (m, 5H), 9.53 ppm (brs, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=$ 25.3, 397.8, 38.0, 40.3, 85.1, 101.5, 128.3, 128.9, 130.1, 131.2, 134.3, 135.0, 145.5, 168.3 ppm; MS (ES^+): m/z: 294 $[M+1]^+$, 316 $[M+Na]^+$; elemental analysis calcd (%) for $C_{14}H_{15}NO_4S$: C 57.32, H 5.15, N 4.77, S 10.93; found: C 57.29, H 5.29, N 4.99, S 11.04.

1,6-Dioxa-4-[(*E*)-2-(methoxycarbonyl)vinyl]amino-2-thiaspiro[4.4]non-3-ene-2,2-dioxide ((*E*)-52) and (*Z*)-52: According to the method described in the journal for the preparation of **12**, a solution of **41** (100 mg, 0.52 mg), methyl propiolate (57 μL, 0.64 mmol) and DMAP (78 mg, 0.64 mmol) in dry acetonitrile (10 mL) was stirred at −20°C for 1.5 h. The solvent was removed and ethyl acetate was added (5 mL) and the mixture was washed with 0.1N HCl (2×5 mL) and brine (2×5 mL). The organic layer was dried, filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2) to give a 93:12 mixture (82 mg, 57%) of (*E*)-**52** and (*Z*)-**52**.

*Data for (E)-**52***: ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=2.29$ (m, 1H), 2.62 (m, 2H), 3.69 (s, 3H), 3.98–4.23 (m, 3H), 5.59 (d, $J=13.8$ Hz, 1H), 6.49 (s, 1H), 7.74 (d, $J=13.8$ Hz, 1H), 8.82 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=38.4$, 52.2, 105.3, 119.8, 141.4, 148.3, 168.3 ppm.

*Data for (Z)-**52***: ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=3.71$ (s, 3H), 5.63 (d, $J=8.0$ Hz, 1H), 6.31 (s, 1H), 6.38 (d, $J=8.0$ Hz, 1H), 9.15 ppm (brs, 1H); MS (ES^+): m/z: 276.3 $[M+1]^+$; elemental analysis calcd (%) for $C_{10}H_{13}NO_6S$: C 43.63, H 4.76, N 5.09, S 11.65; found: C 43.59, H 4.70, N 5.19, S 11.42.

Computational methods: Computational chemistry was carried out by first drawing the molecules in the desktop of Cerius2 and optimising the structures at the AM1 level of theory. Subsequently, electronic energies and structures were calculated by full optimisation, without any geometrical constraint, by using the Becke's three-parameter hybrid functional[24] and using the Lee et al.[25] correlation functional with the 6-31G(d) basis set (B3LYP/6-31G(d)).[26] Frequency calculations were used for all minimised structures to ensure that satisfactory minima were obtained. HOMO energies, zero-point electronic energies and CGhelp charges (CGHelp) were determined by doing a single-point calculation with the hybrid B3LYP/6-31G+(d,f).[27] Semiempirical model (AM1) calculations were performed with MOPAC version 6.0.[28] The Gaussian 03 and Gaussian 98W program packages were used throughout this work.[29] Molecular graphs and pictures were achieved with the GaussView[30] and Arguslab programs.[31]

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