Diastereoselective Dimerisation of Alkenylthiazolines: A Combined Synthetic and Computational Study

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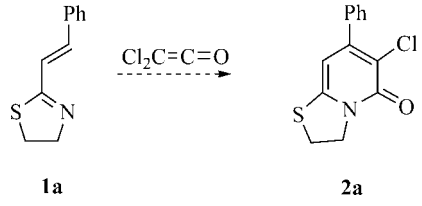
The acylative dimerisation of 2-alkenyl-1,3-thiazolines **1** gives compounds **3** and **8** upon treatment with trichloroacetyl chloride and trifluoroacetic anhydride, respectively. This reaction is completely diastereoselective, in particular giving only a single double-bond isomer. The scope of the reaction has been evaluated synthetically, while a computational study has elucidated the mechanism of the reaction and the origin of stereocontrol.

Introduction

Over the last few years we have investigated the annulation reactions for unsaturated azolines with heterocumulenes.[1] These reactions provide access to a range of novel heterocycles with excellent stereocontrol.[2]

As a continuation of this study we anticipated that reaction of a simple alkenylthiazoline– such as **1a**– with dichloroketene would be followed by loss of HCl to give compound **2a** (Scheme 1). In the event, this reaction turned out to be far from straightforward, and the results of this study are described in full herein.[3]

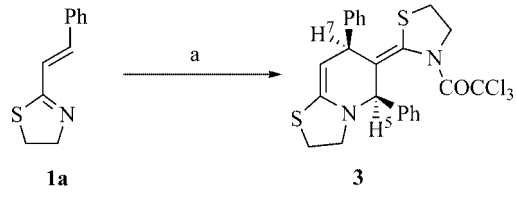


1a **2a**

Scheme 1.

Results and Discussion

When trichloroacetyl chloride was added to a solution of the alkenylthiazoline **1a** containing zinc-copper couple, the expected product **2a** was not obtained. Detailed examination of the spectroscopic data allowed us to propose structure **3** for the product, although we were unable at this stage to elucidate the double-bond geometry. When the reaction was carried out without the zinc-copper couple present, the acylated dimer was formed once again (Scheme 2). From this observation it was clear that the trichloroacetyl chloride was reacting with the thiazoline, and furthermore this acylation was so rapid that in the presence of zinc-copper couple, the ketene did not have time to form. The relatively low yield is a result of losses on chromatography, and we were able to confirm from NMR spectra of the crude reaction products that only a single stereoisomer had been formed. The *cis* relationship between the phenyl rings was initially suggested due to the presence of a 3.5-Hz W-coupling between the two benzylic protons, and was subsequently confirmed by nOe experiments. (Scheme 2).



1a **3**

10% nOe and 3.5 Hz coupling between H^5 and H^7

Scheme 2. a) Cl_3CCOCl, DME, Et_2O, 25 °C, 3 h, 29%.

There appears to be no direct precedent for this transformation, although a related dimerisation of the 2-(benzylideneamino)benzothiazoline **4** to give **5** is known (Scheme 3).[4]

Upon consideration of the possible mechanisms, the formation of a single double-bond isomer is particularly surprising. Reaction of an acylated alkenylthiazoline **6** with compound **1** will ultimately give compound **7**, either by a concerted or stepwise pathway (vide infra). Loss of a proton from this compound will then give the observed product **3**

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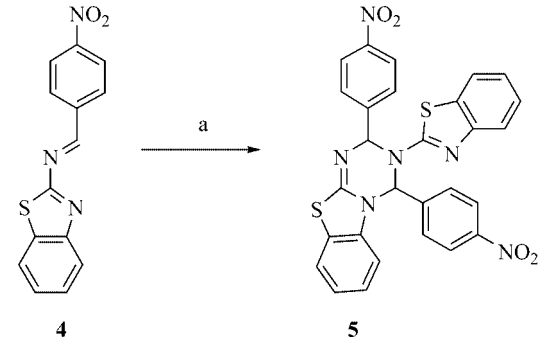
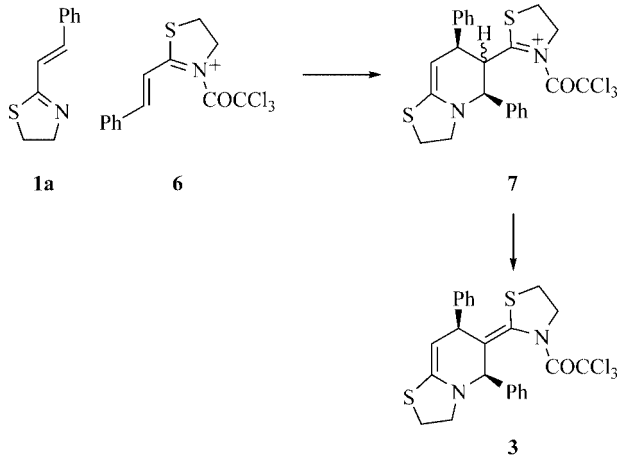


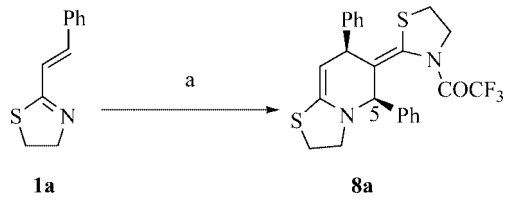
Scheme 3. a) Xylene, reflux, 60 h, 65%.

(Scheme 4). The stereoselective formation of tetrasubstituted double bonds is particularly challenging, and since the environment around the tetrasubstituted double-bond in **3** is almost symmetrical it would be optimistic to expect much stereocontrol in the deprotonation of compound **7**. Indeed, semi-empirical calculations showed that the (*E*) and (*Z*) isomers of compound **8** have negligible differences in energy. We therefore sought to confirm the double-bond geometry and probe the mechanism of this new reaction.



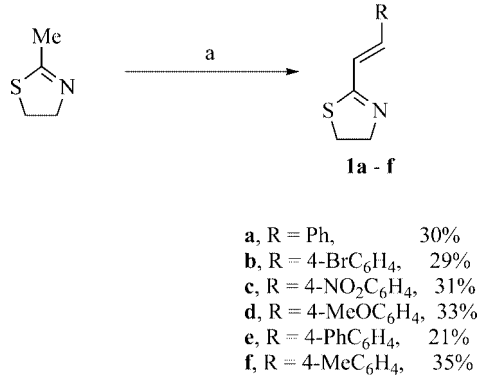
Scheme 4. The basic reaction mechanism.

Despite extensive efforts, compound **3** did not produce crystals suitable for X-ray diffraction. We therefore decided to examine the scope and limitations of the reaction in the hope of producing a crystalline analogue. A range of other acylating agents was screened for their ability to promote the dimerisation of compound **1a**. Triflic anhydride, 4-toluenesulfonyl chloride, acetyl chloride, acetic anhydride and methanesulfonyl chloride returned only starting materials under a variety of conditions. The dimerisation was smoothly induced by trifluoroacetic anhydride, acylated dimer **8a** being formed in 41% yield (Scheme 5). Compared to compound **3**, the 5-H in compound **8a** was shifted approximately 0.5 ppm upfield in the proton NMR spectrum. We tentatively ascribe this as a difference in the through-space effect between the $COCCl_3$ and $COCF_3$ groups; this supports the double-bond geometry shown, although it certainly does not constitute proof.

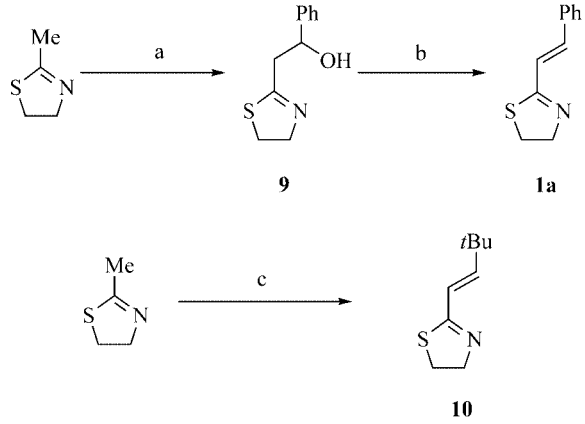


Scheme 5. a) TFAA, DME, Et_2O, 25 °C, 3 h, 41%.

The alkenylthiazolines **1a**–**1f** were prepared by the iodine-catalysed condensation of 2-methylthiazoline with 4-substituted benzaldehydes (Scheme 6). The yields for this reaction, although comparable to those reported in the literature, are modest.[5,6] As an alternative, compounds **1a** and the *tert*-butyl analogue **10** were prepared by a two-step method (Scheme 7).



Scheme 6. a) RC_6H_4CHO, I_2, toluene, reflux, 16 h.

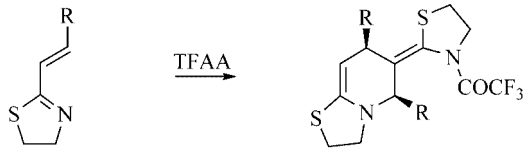


Scheme 7. a) *n*BuLi, THF,–78 °C then PhCHO, 90%; b) TFA, toluene, 4-Å molecular sieves, 1 h, 75%; c) i. *n*BuLi, THF,–78 °C then *t*BuCHO; ii. TFA, toluene, reflux, 3 h, 50% over two steps.

The reaction conditions employed to form the parent compound **8a** were suitable for the 4-methoxyphenyl analogue **8d**, while the 4-bromophenyl, 4-nitrophenyl and 4-phenylphenyl analogues **8b**, **8c** and **8e** called for a change in solvent and elevated temperature (75 °C). The 2-(4-methylphenyl)ethenyl-1,3-thiazoline (**1f**) did not react under any conditions; the *tert*-butyl substrate **10** was also unreactive (Table 1). Within this series, it is impossible to see any trend in either reactivity or yield. We tentatively attribute the lack of reactivity of compound **10** to steric effects, although the

apparent lack of reactivity of compound **1f** is bewildering. None of these compounds gave crystals suitable for X-ray diffraction. The ^{13}C NMR spectroscopic data for these compounds warrant brief comment. It is not surprising, given the anticipated low intensity of quaternary carbons, that the expected quartets for the trifluoroacetamide carbonyl peaks could not be assigned with any degree of confidence. The CF_3 carbon itself in these compounds was also of low intensity, and in the case of compound **8b** was difficult to observe. More surprisingly in all of compounds **8b**, **8c** and **8d** only two distinct aromatic CH peaks were observed in the ^{13}C NMR spectra, whereas the ^1H NMR spectra clearly showed the presence of two different, albeit similar, aromatic rings. Compound **3** also shows only three distinct aromatic CH peaks, and compound **8a** shows four. This coincidence of peaks is unexpected, but all other data (including the aromatic quaternary carbon atoms in the same ^{13}C NMR spectra) are fully consistent with the proposed structures.

Table 1. Acylative dimerisation of 2-alkenyl-1,3-thiazolines.

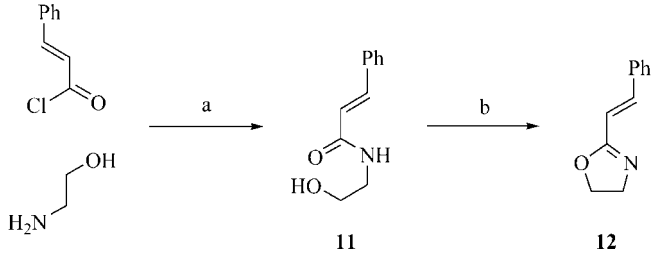


8a - e

Compound	R	Conditions	Yield %
8a	Ph	Et_2O, DME, 25 °C, 3 h	41
8b	4-BrC_6H_4	$CHCl_3$, reflux, 6 h	43
8c	4-$O_2NC_6H_4$	$CHCl_3$, reflux, 3 h	50
8d	4-$MeOC_6H_4$	Et_2O, DME, 25 °C, 3 h	31
8e	4-PhC_6H_4	$CHCl_3$, reflux, 6 h	25[a]

[a] Compound **8e** was obtained with difficulty from a complex mixture and was not obtained analytically pure.

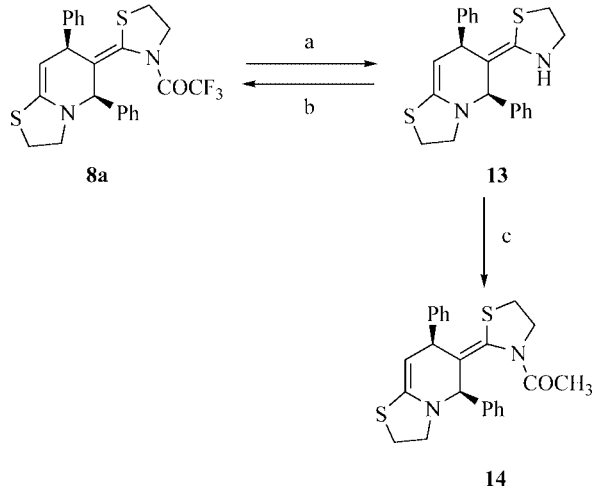
We also briefly investigated whether the reaction could be extended to alkenyloxazolines. The 2-styryl-1,3-oxazoline (**12**) was prepared in two steps from cinnamoyl chloride and ethanolamine via the amide **11** (Scheme 8). This compound failed to react with trifluoroacetic anhydride under any of the conditions used for the corresponding thiazolines.



11 **12**

Scheme 8. a) NaOH, CH_2Cl_2, H_2O, 25 °C, 24 h, 78%; b) MsCl, Et_3N, CH_2Cl_2, 25 °C, 16 h, 90%.

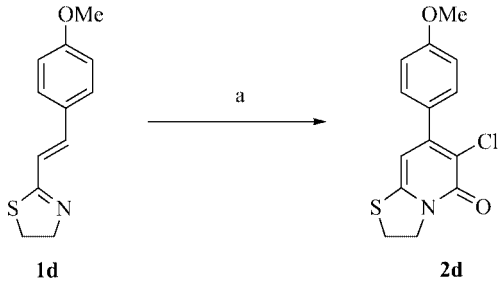
Having failed to prove the double-bond geometry crystallographically, we sought indications of the likely geometry from the NMR spectroscopic data. Apart from the difference in the 5-H between compounds **3** and **8a** mentioned above, the only hint was the upfield shift of two aromatic protons away from the body of the aryl signals, presumably due to the proximity of the trifluoroacetyl group. These were shown by nOe studies to be the *ortho* protons on the phenyl ring at the 5-position, tentatively supporting the double-bond geometry as drawn throughout. It seemed reasonable that upon replacement of the trifluoroacetyl group with an acetyl group a nOe from the acetyl CH_3 to one of the benzylic ring protons might be seen, and the double bond geometry therefore unambiguously proven. The trifluoroacetyl group was cleaved reductively using sodium borohydride, presenting the dimer as the free enamine **13.** This reaction was far from clean and the free enamine was intolerant to chromatography. Re-acylation of this compound with trifluoroacetic anhydride returned an impure sample of **8a** as the same double-bond isomer. Reaction with acetic anhydride gave a very impure sample of the desired compound **14** such that no meaningful nOe data could be obtained (Scheme 9). However, the relative stability and facile acylation of compound **13** appears to preclude an alternative mechanism for the reaction whereby compound **1a** undergoes dimerisation, this being followed by acylation.



8a **13** **14**

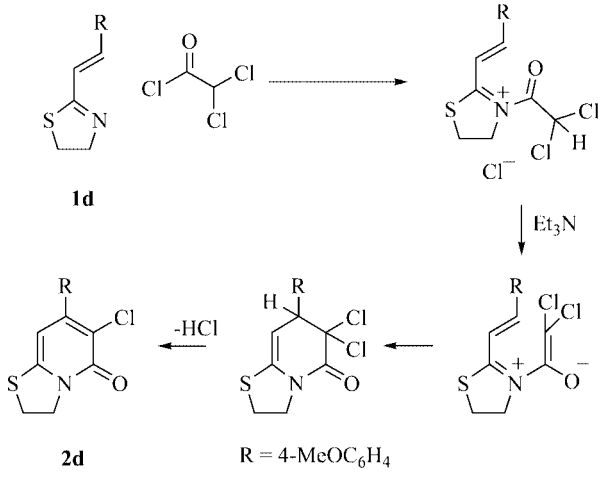
Scheme 9. a) $NaBH_4$, EtOH, 25 °C, 48 h, 80% crude; b) TFAA, Et_3N, DMAP, CH_2Cl_2; c) Ac_2O, DMAP, Et_3N, DMAP, 25 °C, 24 h, see discussion.

Returning to our original synthetic goal, the formation of compounds of general structure **2**, it was clear that while trichloroacetyl chloride is a sufficiently strong electrophile to induce dimerisation of compounds **1**, dichloroacetyl chloride is not. Since dichloroacetyl chloride can be used as a dichloroketene precursor,[7] we added triethylamine to a mixture of compound **1d** and dichloroacetyl chloride in THF. This gave the desired compound **2d** in 89% yield (Scheme 10).[8]



Scheme 10. a) $Cl_2CHCOCl$, Et_3N, THF, 25 °C, 2.5 h, 89%.

This reaction may proceed by attack of **1d** on in situ-generated dichloroketene. However, there is a distinct colour change on addition of dichloroacetyl chloride to **1d**, which leads us to favour reaction between these two species followed by deprotonation and cyclisation as the more likely course of reaction (Scheme 11). Alkenylthiazoline **1a** did not react cleanly under these conditions, possibly reflecting the lower nucleophilicity of this compound.



Scheme 11. Mechanism of formation of compound **2d**.

Computational Studies

Since we had been unable to unequivocally determine the double-bond geometry by chemical and spectroscopic methods, and were unable to rationalise the completely stereoselective formation of a tetrasubstituted double bond in an almost symmetrical local environment, we undertook a computational study of the reaction of compound **1a** with trifluoroacetic anhydride in order to attempt to answer these questions. This study was carried out using the PM3[9] Hamiltonian in the MOPAC program.[10] All calculations were performed with an SCF tolerance of 10^{-6} eV and geometry optimisations and transition state searches used a gradient cut-off of 4 kJ·mol^{-1} Å^{-1}. The potential energy surface for the reaction was searched using a series of constrained optimisations to approximately locate transition states between minima. In the following discussion the degree of freedom constrained will be identified, all other degrees of freedom were optimised at each point of a search. The approximate transition states were optimised using the eigenvector follower approach[11] without constraints and both minima and transition states were confirmed by a frequency analysis at the same level of theory, minima being recognised by a complete set of positive normal modes and transition states by a single negative (imaginary force constant) mode.

The formation of intermediate **7** could proceed via a concerted aza-Diels–Alder pathway, or a stepwise mechanism involving sequential conjugate addition reactions.[12] Proton loss from this compound then leads to the formation of compound **8a**. We initially had reservations about the ability of PM3 calculations to predict the stereochemical outcome of this proton loss. In order to allay these concerns, we elected to calculate the reaction pathway leading to compound **7**, since if we were able to distinguish between concerted and stepwise pathways and rationalise the stereochemistry of this reaction, we could be confident that this level of theory was indeed adequate.

The Concerted Reaction Pathway

This pathway is more straightforward to investigate computationally, as the transition states would be relatively rigid. We investigated both the *exo* and *endo* Diels–Alder pathways for this reaction, but were unable to locate a transition state in either case. These transition states were also unsuccessfully sought using DFT calculations (B3LYP 6-31G** basis set). We were therefore satisfied that the reaction was unlikely to proceed via an initial concerted Diels–Alder pathway, and so turned our attention to the eventually more productive stepwise mechanism. This gave entirely reasonable results which explain all of the stereochemical features of the pathway, and so we are confident that the PM3 level of theory is perfectly adequate in this case.

The Stepwise Reaction Pathway

Since the double-bond geometry is defined in the final abstraction of a proton from an intermediate such as **15**, we examined the barrier to rotation of the acylated thiazoline ring in this compound. The rotational profile is essentially sinusoidal with a substantial barrier to rotation (33 kJ·mol^{-1}). Both minima **15a** and **15b** have similar energies, with the acylated thiazoline ring essentially perpendicular to the bicyclic fragment of the molecule (Figure 1). Therefore, no preference for either clockwise or anticlockwise rotation to give a single product isomer is indicated.

It seemed reasonable that if intermediate **15** was formed in a given conformation, it would be deprotonated to form the final product **8a** rapidly. This would preclude rotation about the C6–C2′ bond and so give rise to a single double-bond isomer. In order to investigate this possibility, we considered all steps in the proposed reaction mechanism in order to understand the conformational bias at each stage. Since much of this study did not eventually shed light

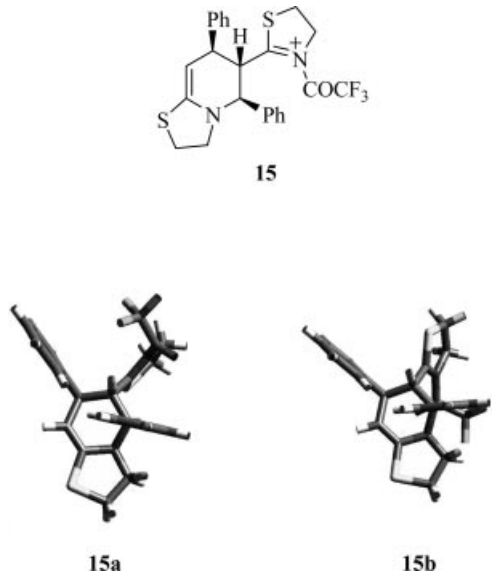


Figure 1. Minimum conformations **15a** and **15b** of intermediate **15**.

on the reason behind the formation of a single double-bond isomer, it will be presented in a condensed form. The *s-trans* conformation **16** of the free thiazoline is slightly favoured (3.5 kJ·mol^{-1}), while after acylation the *s-cis* conformation **17** is more favoured (13 kJ·mol^{-1}) (Figure 2). While these conformations do in fact give rise to the lowest energy transition states and intermediates along the reaction coordinate, the entire reaction pathway was investigated beginning with the *s-cis* and *s-trans* conformers of each.

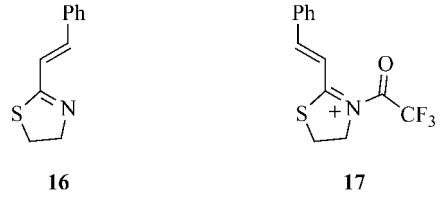
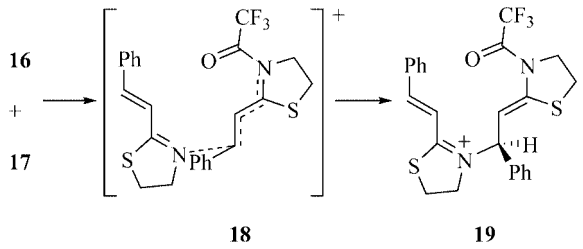


Figure 2.

Location of the transition state **18** for nucleophilic attack of **16** onto **17** proved straightforward. In intermediate **19** the double-bond geometry for the ring closure is fixed (Scheme 12), with the transition state forming the opposite double-bond isomer being 13 kJ·mol^{-1} higher in energy.



Scheme 12.

Of the four possible transition states for the actual ring-closure step, structures **20a** and **20b** are shown schematically in Figure 3. These were located by systematically increasing the corresponding carbon–carbon bond length in the intermediate **15** (Scheme 13) and its rotamer. The analogous transition states to form the 5,7-*anti* diastereomeric transition states were found to be 19 kJ·mol^{-1} and 33 kJ·mol^{-1} higher in energy than **20a** and **20b**, respectively. Therefore, irrespective of the double-bond geometry the 5,7-*syn* arrangement of the phenyl groups is overwhelmingly favoured. It is encouraging that the calculations are able to reproduce this aspect of the experimental observations.

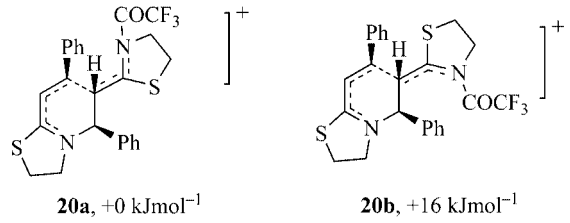
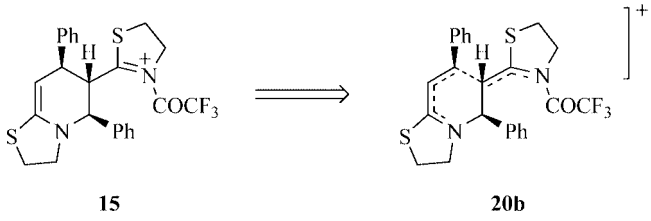


Figure 3.



Scheme 13.

Although these calculations had established the likely conformation of the various intermediates and transition states along the reaction pathway, conformations **15a** and **15b** (of essentially identical energy) were shown to be favoured from **20a** and **20b**, respectively. We therefore still had no basis upon which to predict which double-bond isomer would be formed, or even that any selectivity would be observed. Up to this point the anion for the cationic intermediates had been omitted for simplicity, not least because its location is difficult to determine. However, for the final step of hydrogen abstraction the inclusion of a trifluoroacetate anion to receive the proton was found to be crucial. At this point the positioning of the anion is also less ambiguous since it must be placed with the carboxylate group in close proximity to C6-H. The bulk of the phenyl substituents also place additional limitations on its position. With the anion in place the calculated energy difference between the two intermediate structures **15a**·$CF_3CO_2^-$ and **15b**·$CF_3CO_2^-$ is now significant as shown in Figure 4.

The introduction of the anion causes significant conformational change of the phenyl substituents to allow its interaction with the C6 proton. This change is more notable at the 5-phenyl than the 7-phenyl which is held more rigidly in place by the C=C bond of the six membered heterocycle. However the C6-H and C–N bonds are still found to be near co-planar and so the geometry of the product double bond is still ambiguous at this stage. Transition states for the proton removal were located using two methods. Firstly a series of constrained optimisations with the C6-H bond length systematically increased was explored and secondly

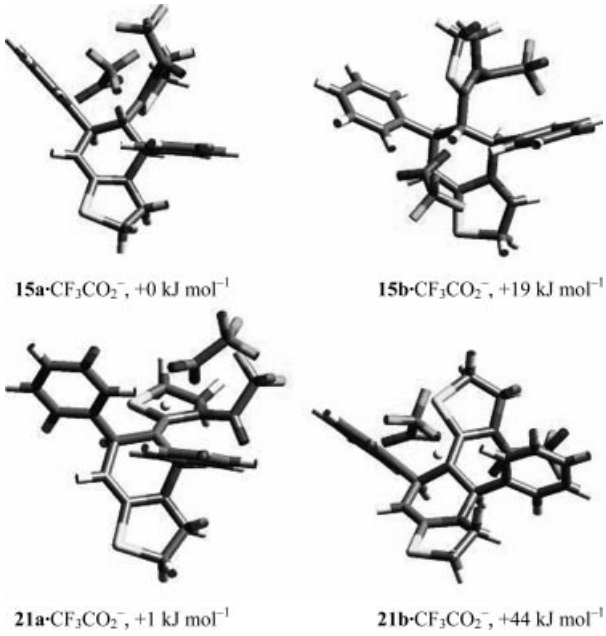


Figure 4.

by rotation of the acylated thiazoline ring from each of the intermediates **15a**·$CF_3CO_2^-$ and **15b**·$CF_3CO_2^-$ without constraining the C6-H distance. Both approaches led to the same conclusion that proton loss occurs as the five-membered ring rotates to become co–planar with the six–membered heterocycle, so that the formation of the new double bond occurs simultaneously with proton loss to form the neutral acylated dimer. From **15a**·$CF_3CO_2^-$ we obtained the preferred transition state **21a** and from **15b**·$CF_3CO_2^-$ the transition state **21b** was located. Both structures therefore lead to the same (*E*) double bond isomer. Rotational searches to find the corresponding (*Z*) isomer failed since the steric hindrance between the trifluoroacetyl group and the 7-phenyl prevented the five-membered ring rotating to become co-planar with the piperidine ring. It appears, then, that selectivity is controlled by the ease of rotation of the acylated thiazoline ring to form the new C=C bond. This is impeded by steric interactions between the trifluoroacetyl group and the phenyl substituents. In the case of the (*Z*) isomer, the 7-phenyl group has less conformational mobility so that rotation to give the (*E*) isomer is the preferred process.

Conclusions

A novel stereoselective acylative dimerisation reaction of alkenylthiazolines has been investigated experimentally and computationally. The calculations show the importance of including counterions in the structure in order to fully explain the stereoselectivity in such reactions.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded with a Fisons VG Platform II spectrometer. High-resolution mass spectra were performed at the EPSRC centre for Mass Spectroscopy in Swansea. NMR spectra were recorded at 25 °C with a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C or with a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR is reported as singlet (s), doublet (d), double doublet (dd), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using matrex silica 60 35–70 micron.

4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-thiazole (1a): 2-Methylthiazoline (5.06 g, 50 mmol), and benzaldehyde (5.36 g, 50.0 mol) were heated under reflux in toluene (50 mL) under Dean–Stark conditions. After 1 h iodine (100 mg) was added and reflux allowed to continue for 16 h. The reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the solvent removed in vacuo. The resulting thick oil was dissolved in diethyl ether and filtered, the filtrate was concentrated in vacuo and distilled under reduced pressure (kugelrohr, oven temperature 180 °C at 0.5 Torr), to give **1a** (2.8 g, 30%) as a white crystalline solid, m.p. 103–105 °C (ref.[6] m.p. 101–102 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1583, 1462, 1377 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.43 [dd, ^3J(H,H) = 7.9, $^4J_{H,H}$ = 1.3, 2 H, aromatic C*H*], 7.40–7.25 (m, 3 H, aromatic C*H*), 7.05 (d, $^3J_{H,H}$ = 16.2, 1 H, one of alkene C*H*), 6.95 (d, $^3J_{H,H}$ = 16.2, 1 H, one of alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.25 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 141.6 (alkene *C*H), 135.7 (aromatic *C*), 129.8 (aromatic *C*H) 129.3 (aromatic *C*H), 127.9 (aromatic *C*H), 123.1 (alkene *C*H), 65.1 (*C*H_2N), 33.4 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 190 (100) [M + H]$^+$.

2-[(*E*)-2-(4-Bromophenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1b): 2-Methylthiazoline (2.2 g, 20 mmol) and 4-bromobenzaldehyde (3.6 g, 20 mmol), were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The resulting reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the solvent removed in vacuo. The dark oil resulting was dissolved in diethyl ether (40 mL) and filtered. The diethyl ether was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with diethyl ether/CH_2Cl_2, 1:9), late fractions yielding **1b** (1.6 g, 30%) as a white solid; m.p. 160–163 °C. IR ($CDCl_3$): $\tilde{\nu}$ = 1634, 1574, 1489, 1007 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.39 (d, $^3J_{H,H}$ = 7.4, 2 H, aromatic C*H*), 7.29 (d, $^3J_{H,H}$ = 7.4, 2 H, aromatic C*H*), 6.95 (apparent s, 2 H, 2 × alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.0, 2 H, CH_2N), 3.25 (t, $^3J_{H,H}$ = 8.0, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.0 (thiazoline *C*), 140.1 (alkene *C*H), 134.7 (aromatic *C*) 132.5 (aromatic *C*H), 129.3 (aromatic *C*H), 123.9 (aromatic *C*), 123.7 (alkene *C*H), 65.2 (*C*H_2N), 33.5 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 270 (100) [M + H]$^+$, 268 (100) [M + H]$^+$, 71 (58). HRMS (CI) $C_{11}H_{11}{}^{79}BrNS$ [M + H]$^+$: 267.9795; found 267.9797.

4,5-Dihydro-2-[(*E*)-2-(4-nitrophenyl)ethenyl]-1,3-thiazole (1c): 2-Methylthiazoline (2.20 g, 20 mmol) and 4-nitrobenzaldehyde (3.0 g, 22 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with sodium thiosulfate solution (100 mL), dried with $MgSO_4$ and the toluene removed in vacuo. Diethyl ether (40 mL) was added to

the resulting dark oil, and **1c** (1.45 g, 31%) isolated by filtration as a light brown solid; m.p. 213–216 °C, (ref.[6] m.p. 214–216 °C) which was used without further purification. IR (CH_2Cl_2): $\tilde{\nu}$= 1629, 1604, 1508, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.25 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 7.64 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 7.17 (d, $^3J_{H,H}$ = 16.4, 1 H, one of alkene C*H*), 7.10 (d, $^3J_{H,H}$ = 16.4, 1 H, one of alkene C*H*), 4.40 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.35 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.6 (thiazoline *C*), 148.3 (aromatic *C*), 141.9 (aromatic *C*), 139.5 (alkene *C*H), 128.3 (aromatic *C*H), 127.1 (alkene *C*H), 124.6 (aromatic *C*H), 65.4 (*C*H_2N), 33.7 (*C*H_2S) ppm. MS (ammonia CI): *m*/*z* (%) = 235 (26) [M + H]$^+$, 220 (33), 205 (100). HRMS (CI) $C_{11}H_{11}N_2O_2S$ [M + H]$^+$: 235.0541; found 235.0545.

4,5-Dihydro-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,3-thiazole (1d): 2-Methylthiazoline (2.5 g, 25 mmol) and 4-methoxybenzaldehyde (2.8 g, 24 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (50 mg) was added and the reflux continued for 18 h. The resulting brown solution was washed with saturated sodium thiosulfate solution (50 mL), dried with $MgSO_4$ and the solvent removed in vacuo. The brown oil remaining was dissolved in diethyl ether (30 mL), filtered and the diethyl ether was removed in vacuo, to yield a brown solid which was purified by column chromatography (eluting with diethyl ether) late fractions yielding **1d** (1.8 g, 33%,) as colourless plates, m.p. 100–102 °C (ref.[6] m.p. 99–101 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1463, 1377 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 7.07 (d, $^3J_{H,H}$ = 16.1, 1 H, one of alkene C*H*), 6.93 (d, $^3J_{H,H}$ = 16.1, 1 H, one of alkene C*H*), 6.89 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 4.35 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2N), 3.85 (s, 3 H, OCH_3), 3.30 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2S) ppm. ^{13}C NMR (125 MHz. $CDCl_3$, 25 °C): δ = 168.5 (thiazoline *C*), 160.8 (aromatic *C*), 141.2 (alkene *C*H), 129.1 (aromatic *C*H), 128.0 (aromatic C), 120.2 (alkene *C*H), 114.3 (aromatic *C*H), 64.3 (*C*H_2N) 55.4 (O*C*H_3), 32.9 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 220 (100) [M + H]$^+$.

2-[(*E*)-2-(4-Phenylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1e): 2-Methylthiazoline (1.75 g, 17 mmol) and 4-phenylbenzaldehyde (3.15 g, 17 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with saturated sodium thiosulfate solution (100 mL), dried with $MgSO_4$, and the toluene removed in vacuo. The resulting dark oil was dissolved in diethyl ether (40 mL) and filtered. The diethyl ether was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with CH_2Cl_2), late fractions yielding **1e** (960 mg, 21%) as an off-white crystalline solid, m.p. 141–144 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1633, 1582, 1488, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.74–7.56 (m, 6 H, aromatic C*H*), 7.46 (apparent t, $^3J_{H,H}$ = 7.5, 2 H, aromatic C*H*), 7.36 (t, $^3J_{H,H}$ = 7.4, 1 H, aromatic C*H*), 7.26 (d, $^3J_{H,H}$ = 16.2, 1 H, alkene C*H*), 7.08 (d, $^3J_{H,H}$ = 16.2, 1 H, alkene C*H*), 4.40 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2N), 3.36 (t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 142.2 (aromatic *C*), 141.1 (alkene *C*H), 140.7 (aromatic *C*), 134.7 (aromatic *C*), 129.3, 128.3, 128.1, 127.9 and 127.4 (all aromatic *C*H), 123.0 (alkene *C*H), 65.2 (*C*H_2N), 33.5 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 266 (100) [M + H]$^+$. HRMS (CI) $C_{17}H_{16}NS$ [M + H]$^+$: 266.1003; found 266.0997.

2-[(*E*)-2-(4-Methylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (1f): 2-Methylthiazoline (2.5 g, 25 mmol) and 4-tolualdehyde (2.84 g, 25 mmol) were heated under reflux in toluene (100 mL) under Dean–Stark conditions for 1 h. Iodine (100 mg) was added and the reflux continued for 16 h. The reaction mixture was washed with saturated sodium sulfite solution (40 mL). The solvent was removed in vacuo to give a brown solid which was purified by column chromatography (eluting with CH_2Cl_2), late fractions affording **1e** (1.8 g, 35%) as a white solid, m.p. 148–150 °C (ref.[6] m.p. 148–150 °C). IR (CH_2Cl_2): $\tilde{\nu}$ = 1634, 1579, 1318, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, $^3J_{H,H}$ = 8.0, 2 H, aromatic C*H*), 7.11 (d, $^3J_{H,H}$ = 8.0, 2 H, aromatic C*H*), 6.99 (d, $^3J_{H,H}$ = 15.8, 1 H, one of alkene C*H*), 6.93 (d, $^3J_{H,H}$ = 15.8, 1 H, one of alkene C*H*), 4.30 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2N), 3.26 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2S), 2.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.3 (thiazoline *C*), 141.6 (alkene *C*H), 140.1 (aromatic *C*), 133.0 (aromatic *C*), 130.0 and 127.8 (aromatic *C*H), 122.1 (alkene *C*H), 65.1 (*C*H_2N), 33.4 (*C*H_2S), 21.8 (*C*H_3) ppm. MS (APCI): *m*/*z* (%) = 204 (100) [M + H]$^+$.

6-Chloro-2,3-dihydro-7-(4-methoxyphenyl)-5*H*-[1,3]thiazolo[3,2-*a*]-pyridin-5-one (2d): 4,5-Dihydro-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,3-thiazole (**1d**) (520 mg, 2.4 mmol) was dissolved in dry THF (8 mL). Dichloroacetyl chloride (230 μL, 2.24 mmol) was added and the resulting bright red mixture stirred at 25 °C under N_2 for 20 min. Triethylamine (340 μL, 2.4 mmol) was added and the resulting cloudy brown mixture stirred for a further 2 h. The resulting suspension was filtered and the filtrate dried with $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (eluting with diethyl ether/CH_2Cl_2, 1:5) yielded **2d** (625 mg, 89%) as a light brown solid m.p. 128–130 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1636, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 6.87 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 6.15 (s, 1 H, 8-*H*), 4.52 (d, $^3J_{H,H}$ = 7.4, 2 H, CH_2N), 3.79 (s, 3 H, OCH_3), 3.41 (t, $^3J_{H,H}$ = 7.4, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 159.0 (*C*=O), 157.6 (S*C*N), 149.6 (*C*Cl), 144.4 (aromatic *C*), 128.9 (aromatic *C*H), 128.3 (aromatic *C*), 116.7 (aromatic *C*), 112.7 (aromatic *C*H), 101.4 (8-*C*), 52.3 (O*C*H_3), 50.8 (*C*H_2N), 27.9 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 296 (35) [M + H]$^+$, 294 (100) [M + H]$^+$. HRMS (CI) $C_{12}H_{13}NO_4S^{35}Cl$ [M + H]$^+$: 294.0355; found 294.0359.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trichloroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (3): 4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-thiazole (**1a**) (250 mg, 1.3 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trichloroacetyl chloride (15 μL, 0.8 mmol) was added dropwise with stirring under N_2 at 25 °C. The reaction mixture was stirred for 3 h, washed with aqueous $NaHCO_3$ solution (10 mL) then with brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to yield a glassy orange solid, which was purified by chromatography on neutral alumina (eluting with CH_2Cl_2) late fractions yielding compound **3** as a colourless solid (98 mg, 29%), m.p. 186–188 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 1691, 1625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.20–7.10 (m, 8 H, aromatic C*H*), 6.90 (m, 2 H, aromatic C*H*), 5.05 (d, $^4J_{H,H}$ = 3.5, 1 H, 5-*H*), 4.55 (d, $^3J_{H,H}$ = 11.8, 1 H, alkene C*H*), 3.95–3.85 (m, 2 H, CH_2NCO), 3.50–3.35 (m, 3 H, 7-*H* and CH_2N), 3.10–2.95 (m, 2 H, CH_2S), 2.90–2.80 (m, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 175.6 (*C*=O), 168.7, 167.2 (both thiazoline *C*), 139.6 and 138.7 (aromatic *C*), 128.5, 127.8, 127.2 (all aromatic *C*H), 97.5 (CCl_3), 96.7 (alkene *C*), 64.5 (*C*H_2NCO), 60.5 (alkene *C*H), 52.9 (*C*H_2N), 50.0 (5-*C*), 43.6 (7-*C*), 33.3 (*C*H_2S), 27.0 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 525 (9) [M + H]$^+$, 523 (10) [M + H]$^+$, 190 (100) [M + H]$^+$ (molecular ion shows expected isotopic distribution pattern). HRMS (CI) $C_{24}H_{22}{}^{35}Cl_3N_2O_2S$ [M + H]$^+$: 523.0239; found 523.0240.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (8a): 2-[(*E*)-2-Phenylethenyl]-4,5-dihydro-1,3-thiazole (**1a**) (150 mg, 0.8 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trifluoroacetic anhydride (70 μL, 0.5 mmol) was added dropwise with stirring under N_2 at 25 °C. The reaction mixture was stirred for 3 h, washed with aqueous $NaHCO_3$ solution (10 mL) then with brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to yield a glassy orange solid, which was purified by chromatography on neutral alumina (eluting with CH_2Cl_2), late fractions yielding **8a** (78 mg, 41%) as a white solid, m.p. 196–198 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1691, 1625, 1499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.12 (m, 8 H, aromatic C*H*), 6.85 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.7, 2 H, aromatic C*H*), 4.56 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.51 (d, $^4J_{H,H}$ = 4.2, 1 H, 5-*H*), 3.79 (m, 2 H, CH_2NCO), 3.41 (dd, $^3J_{H,H}$ = 11.1, $^4J_{H,H}$ = 4.2, 1 H, 7-*H*), 3.35–3.30 (m, 2 H, CH_2N), 3.00–2.80 (m, 4 H, 2×SCH_2) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 166.5 and 164.6 (both thiazoline *C*), 139.5 and 136.9 (both aromatic *C*), 127.6, 127.1, 126.9, 126.3 (all aromatic *C*H), 117.1 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 97.9 (alkene *C*), 70.7 (NCO*C*H_2), 59.1 (alkene *C*H), 51.8 (N*C*H_2), 48.8 (5-*C*), 40.7 (7-*C*), 32.3 (*C*H_2S), 29.2 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 475 (100) $[M + H]^+$, 102.5 (29). HRMS (EI) $C_{24}H_{22}F_3N_2OS_2$ $[M + H]^+$: 475.1127; found 475.1125.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-bromophenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8b): 2-[(*E*)-2-(4-Bromophenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1b**) (200 mg, 0.74 mmol), was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (75 μL, 0.53 mmol) was added dropwise and the reaction mixture heated under reflux for 6 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL) then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a light brown solid which was purified by column chromatography on alumina (eluting with CH_2Cl_2) early fractions yielding **8b** (100 mg, 43%) as a white solid, m.p. 200–203 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1692, 1625, 1500, 1464 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, $^3J_{H,H}$ = 8.4, 2 H, aromatic CH), 7.30 (d, $^3J_{H,H}$ = 8.4, 2 H, aromatic CH), 7.08 (d, $^3J_{H,H}$ = 8.5, 2 H, aromatic CH), 6.73 (d, $^3J_{H,H}$ = 8.5, 2 H, aromatic C*H*), 4.50 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene *C*H), 4.47 (d, $^4J_{H,H}$ = 4.2, 1 H, 5-*H*), 3.80 (apparent t, $^3J_{H,H}$ = 8.3, 2 H, CH_2NCO), 3.40–3.30 (m, 3 H, 7-*H* and CH_2N), 3.11–3.03 (m, 2 H, CH_2S), 2.95–2.88 (m, 2 H, CH_2S) ppm. ^{13}C NMR (125 MHz. $CDCl_3$, 25 °C): δ = 166.5 and 165.8 (both thiazoline *C*), 138.4 and 136.0 (both aromatic *C*), 130.1, 128.6 (both aromatic *C*H), 121.7, 120.3 (both *C*–Br), 97.5 (alkene *C*), 63.2 (*C*H_2NCO), 58.5 (alkene *C*H), 51.8 (N*C*H_2), 48.4 (5-*C*), 40.0 (7-*C*), 32.4 (S*C*H_2), 26.2 (S*C*H_2) ppm. MS (APCI): *m*/*z* (%) = 635 (58) $[M + H]^+$, 633 (100) $[M + H]^+$, 631 (48) $[M + H]^+$. HRMS (CI) $C_{24}H_{19}{}^{79}Br_2F_3N_2OS_2$ $[M + H]^+$: 630.9336; found 630.9335.

(5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-bis(4-nitrophenyl)[1,3]thiazolo[3,2-*a*]pyridine (8c): 4,5-Dihydro-2-[(*E*)-2-(4-nitrophenyl)ethenyl]-1,3-thiazole (**1c**) (200 mg, 0.85 mmol) was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (83 μL, 0.6 mmol) was added dropwise and the solution heated under reflux for 3 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a yellow solid which was purified by flash chromatography on alumina (eluting with CH_2Cl_2), yielding **8c** (120 mg, 50%) as a pale yellow solid, m.p. 210–212 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1683, 1625, 1462 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (d, $^3J_{H,H}$ = 8.3, 2 H, aromatic C*H*), 8.09 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 7.40 (d, $^3J_{H,H}$ = 8.6, 2 H, aromatic C*H*), 7.06 (d, $^3J_{H,H}$ = 8.7, 2 H, aromatic C*H*), 4.66 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.61 (d, $^4J_{H,H}$ = 4.1, 1 H, 5-*H*), 3.71–3.65 (m, 2 H, CH_2NCO), 3.49 (dd, $^3J_{H,H}$ = 11.1, $^4J_{H,H}$ = 4.1, 1 H, 7-*H*), 3.45–3.40 (m, 1 H, one of CH_2N) 3.31 (ddd, $^2J_{H,H}$ = 10.6, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 2.9, 1 H, one of CH_2N), 3.17–2.98 (m, 4 H, 2×CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 168.4, 166.7 (both thiazoline *C*), 148.5, 148.1, 147.7, 145.4 (all aromatic *C*), 129.2, 123.8 (both aromatic *C*H), 118.1 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 98.2 (alkene *C*), 64.7 (*C*H_2NCO), 59.7 (alkene *C*H), 53.3 (*C*H_2N), 49.6 (5-*C*), 41.7 (7-*C*), 33.9 (*C*H_2S), 27.7 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 565 (100) $[M + H]^+$, 65 (57). HRMS (CI) $C_{24}H_{20}N_4O_5F_3S_2$ $[M + H]^+$: 565.0828; found 565.0857.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-methoxyphenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8d): 2-[(*E*)-2-(4-Methoxyphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1d**) (200 mg, 0.93 mmol) was dissolved in dry diethyl ether (1 mL) and dry DME (4 mL). Trifluoroacetic anhydride (90 μL, 0.64 mmol) was added dropwise and the solution stirred under N_2 at 25 °C for 3 h. The orange solution resulting was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give an orange solid which was purified by flash chromatography on alumina (eluting with CH_2Cl_2) yielding **8d** (77 mg, 31%) as a pale yellow solid; m.p. 183–185 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 1683, 1624, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.10 (d, $^3J_{H,H}$ = 8.8, 2 H, aromatic C*H*), 6.80–6.69 (m, 6 H, aromatic C*H*), 4.52 (d, $^3J_{H,H}$ = 11.1, 1 H, alkene C*H*), 4.45 (d, $^4J_{H,H}$ = 3.9, 1 H, 5-*H*), 3.83 (m, 2 H, CH_2NCO), 3.72 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.40 (m, 3 H, CH_2N and 7-*H*), 3.05 (m, 2 H, CH_2S), 2.93 (m, 2 H, CH_2S) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 167.9, 167.7 (both thiazoline *C*), 160.0, 158.9, 133.0, 130.2 (all aromatic *C*), 129.5 (aromatic *C*H), 118.0 (q, $^1J_{C,F}$ = 290 Hz, *C*F_3), 113.6 (aromatic *C*H), 99.7 (alkene *C*), 64.6 (*C*H_2NCO), 60.1 (alkene *C*H), 55.6 (OCH_3), 55.4 (OCH_3), 53.2 (*C*H_2N), 50.4 (5-*C*), 41.1 (7-*C*), 33.7 (*C*H_2S), 27.6 (*C*H_2S) ppm. MS (APCI): *m*/*z* (%) = 535 (100) $[M + H]^+$. HRMS (EI) $C_{24}H_{20}N_4O_5F_3S_2$ $[M]^+$: 534.1259; found 534.1260.

(5*RS*,7*RS*,*E*)-2,3,5,7-Tetrahydro-5,7-bis(4-phenylphenyl)-6-(4,5-dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)[1,3]thiazolo[3,2-*a*]pyridine (8e): 2-[(*E*)-2-(4-Phenylphenyl)ethenyl]-4,5-dihydro-1,3-thiazole (**1e**) (150 mg, 0.57 mmol) was dissolved in dry chloroform (5 mL). Trifluoroacetic anhydride (70 μL, 0.5 mmol) was added dropwise and the solution heated under reflux for 6 h. The resulting orange solution was washed with aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a yellow solid which was purified twice by flash chromatography on alumina (eluting with CH_2Cl_2), yielding **8e** (45 mg, 25%) as a pale yellow solid. This compound exhibited spectroscopic data in line with compounds **8a**–**8d**, but could not be purified to allow full characterisation.

2-(4,5-Dihydro-1,3-thiazol-2-yl)-1-phenyl-1-ethanol (9):[13] 2-Methylthiazoline (2.0 g, 20 mmol) was dissolved in dry THF and cooled to–78 °C. *n*-Butyllithium (8.7 mL of a 2.5 M solution in hexanes, 22 mmol) was added and the resulting orange solution stirred at–78 °C under N_2 for 1 h. Benzaldehyde (2.1 g, 20 mmol) was added and the reaction mixture stirred for a further 2 h at–78 °C then allowed to warm to 25 °C over 1 h. Saturated ammonium chloride solution (20 mL) was added, and the products extracted with diethyl ether (3×30 mL), the organic portions were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to give compound **9** (3.6 g, 90%) as an orange solid, m.p. 76–79 °C

(dec.). IR (CH_2Cl_2): $\tilde{\nu}$ = 3267, 1624, 1434, 1124 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30 (apparent t, $^3J_{H,H}$ = 7.5, 2 H, aromatic CH), 7.26 (d, $^3J_{H,H}$ = 7.6, 2 H, aromatic CH), 7.19 (t, $^3J_{H,H}$ = 6.9, 1 H, aromatic C*H*), 5.04 (apparent t, $^3J_{H,H}$ = 6.3, 1 H, C*H*OH), 4.70 (broad s, 1 H, O*H*), 4.18 (m, 2 H, CH_2N), 3.21 (apparent t, $^3J_{H,H}$ = 8.2, 2 H, CH_2S), 2.72 (m, 2 H, CH_2CHOH) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 171.0 (thiazoline *C*), 142.3 (aromatic *C*), 128.8, 128.0 and 126.2 (aromatic *C*H), 71.8 (*C*HOH), 64.6 (*C*H_2N), 43.1 (*C*H_2S), 33.8 (*C*H_2CHOH) ppm. MS (APCI): *m*/*z* (%) = 208 (40) $[M + H]^+$, 190 (100).

Alternative Preparation of 2-[(*E*)-2-Phenylethenyl]-4,5-dihydro-1,3-thiazole (1a): 2-(4,5-Dihydro-1,3-thiazol-2-yl)-1-phenyl-1-ethanol (**9**) (1.5 g, 7.2 mmol) was dissolved in toluene (15 mL). Trifluoroacetic acid (2 drops) was added followed by 4-Å molecular sieves, and the mixture heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (50 mL), washed with water (50 mL) and brine (50 mL). The resulting solution was dried with $MgSO_4$ and the solvent removed in vacuo to give an orange solid which was purified by kugelrohr distillation (180 °C, 0.5 Torr) to give the title compound (1.03 g, 75%) as a colourless solid. Data were as previously reported.

4,5-Dihydro-2-[(*E*)-3,3-dimethyl-1-butenyl]-1,3-thiazole (10): 2-Methylthiazoline (2.5 g, 25 mmol) was dissolved in THF (15 mL) and cooled to–78 °C. *n*-Butyllithium (7.8 mL of a 2.5 M solution in hexanes, 26 mmol) was added dropwise and the resulting orange anion was stirred for 30 min. 2,2-(Dimethyl)propionaldehyde (1.86 g, 21 mmol) was then added dropwise and the clear orange solution resulting was stirred for 1 h at–78 °C then warmed to 25 °C over 2 h. Water (20 mL) was then added, and the organic layer separated, the aqueous layers was extracted with diethyl ether (3 × 20 mL). The combined organic layers were concentrated in vacuo. The resulting red solid was dissolved in toluene (40 mL), trifluoroacetic acid (30 mg) was added and the mixture heated under reflux, under Dean–Stark conditions for 1 h. The brown solution remaining was washed with saturated sodium hydroxide solution (30 mL), dried with $MgSO_4$, and the solvent removed in vacuo to yield the essentially pure **10** (2.1 g, 50%) as a yellow oil. IR (CH_2Cl_2): $\tilde{\nu}$ = 1647, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.26 (d, $^3J_{H,H}$ = 15.3, 1 H, one of alkene C*H*), 6.23 (d, $^3J_{H,H}$ = 15.3, 1 H, one of alkene C*H*), 4.24 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2N), 3.20 (t, $^3J_{H,H}$ = 8.1, 2 H, CH_2S), 1.03 (s, 9 H 3 × CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 171.7 (thiazoline *C*), 155.2 (alkene *C*H), 120.6 (alkene *C*H), 64.5 (*C*H_2N), 34.0 [*C*$(CH_3)_3$], 32.8 (*C*H_2S), 29.0 (3 × *C*H_3) ppm. MS (APCI): *m*/*z* (%) = 170 (100) $[M + H]^+$. HRMS (CI) $C_8H_{16}NS$ $[M + H]^+$: 170.1003; found 170.1000.

(*E*)-*N*-(2-Hydroxyethyl)-3-phenyl-2-propenamide (11): (*E*)-Cinnamoyl chloride (1.0 g, 6 mmol) and ethanolamine (336 mg, 6 mmol) were dissolved in CH_2Cl_2 (20 mL). A saturated solution of sodium carbonate (54 mL) was added and the mixture stirred at 25 °C for 16 h. Brine was added and the products extracted into CH_2Cl_2 (3 × 30 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a white solid. Recrystallisation from ethyl acetate gave compound **11** (0.91 g, 78%) as a white crystalline solid, m.p. 67–69 °C (ref.[14] m.p. 67–68 °C). IR: ν (melt) = 3298, 1650, 1597 1556, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.60 (d, $^3J_{H,H}$ = 15.6, 1 H, alkene C*H*), 7.55 (m, 2 H, aromatic C*H*), 7.25 (m, 3 H, aromatic C*H*), 6.37 (d, $^3J_{H,H}$ = 15.6, 1 H, alkene C*H*), 6.30 (broad s, 1 H, N*H*), 3.75 (m, 2 H, CH_2O), 3.52 (m, 2 H, CH_2N), 3.00 (broad s, 1 H, O*H*) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 167.6 (amide *C*=O), 142.0 (alkene CH), 135.0 (aromatic *C*), 130.3 (aromatic *C*H), 129.3 (aromatic *C*H), 128.3 (aromatic *C*H), 120.6 (alkene *C*H), 62.7 (*C*H_2O), 43.1 (*C*H_2N) ppm. MS (APCI): *m*/*z* (%) = 192 (100) $[M + H]^+$.

4,5-Dihydro-2-[(*E*)-2-phenylethenyl]-1,3-oxazole (12): (*E*)-*N*-(2-Hydroxyethyl)-3-phenyl-2-propenamide (**11**) (1.1 g 5.75 mmol), was dissolved in CH_2Cl_2 (50 mL), triethylamine (580 mg, 5.75 mmol) was added and the mixture cooled to 0 °C. Methanesulfonyl chloride (665 mg, 5.75 mmol) was added and the resulting solution stirred at 25 °C for 24 h. The reaction mixture was washed with $NaHCO_3$ solution (10 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a green oil which was purified by column chromatography (eluting with ethyl acetate/diethyl ether, 1:10), early fractions yielding compound **12** (895 mg, 90%) as a white solid, m.p. 51–54 °C (ref.[15] m.p. 53–55 °C). IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 1651, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28 (d, $^3J_{H,H}$ = 7.6, 2 H, aromatic C*H*), 7.21–7.08 (m, 4 H, aromatic C*H* and one of alkene C*H*), 6.43 (d, $^3J_{H,H}$ = 15.1, 1 H, alkene C*H*), 4.13 (t, $^3J_{H,H}$ = 9.3, 2 H, CH_2N), 3.79 (t, $^3J_{H,H}$ = 9.3, 2 H, CH_2O) ppm. ^{13}C NMR (100 MHz. $CDCl_3$, 25 °C): δ = 166.2 (oxazoline *C*), 140.2 (alkene *C*H), 135.6 (aromatic *C*), 129.8, 129.2 and 127.9 (all aromatic *C*H), 115.5 (alkene *C*H), 67.6 (*C*H_2O), 55.3 (*C*H_2N) ppm. MS (APCI): *m*/*z* (%) = 174 (100) $[M + H]^+$.

(5*RS*,7*RS*,*E*)-5,7-Diphenyl-6-(4,5-dihydro-1,3-thiazol-2-ylidene)-2,3,6,7-tetrahydro[1,3]thiazolo[3,2-*a*]pyridine (13): (5*RS*,7*RS*,*E*)-6-(4,5-Dihydro-3-trifluoroacetyl-1,3-thiazol-2-ylidene)-2,3,5,7-tetrahydro-5,7-diphenyl[1,3]thiazolo[3,2-*a*]pyridine (**8a**) (200 mg, 0.4 mmol) was dissolved in ethanol (10 mL). Sodium borohydride (30 mg, 0.8 mmol) was added and the mixture stirred at 25 °C for 24 h. Water (10 mL) and DCM (10 mL) were added and the phases separated. The organic phase was dried with $MgSO_4$, and concentrated in vacuo to give compound **13** (127 mg, 80%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.15 (m, 10 H, aromatic C*H*), 4.29 (d, $^3J_{H,H}$ = 11.3, 1 H, alkene C*H*), 4.11 (d, $^4J_{H,H}$ = 5.1, 1 H, 5-*H*), 3.60 (m, 2 H, CH_2N), 3.49 (dd, $^3J_{H,H}$ = 11.3, $^4J_{H,H}$ = 5.1, 1 H, 7-*H*), 3.21–2.99 (m, 4 H, CH_2N and CH_2S), 2.80 (t, $^3J_{H,H}$ = 8.5, 2 H, CH_2S) ppm.

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