Tetrahedron 68 (2012) 5863–5881

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

CuCl-catalyzed radical cyclisation of *N*-α-perchloroacyl-ketene-*N*,*S*-acetals: a new way to prepare disubstituted maleic anhydrides

Andrea Cornia [a], Fulvia Felluga [b], Vincenzo Frenna [c], Franco Ghelfi [a,*], Andrew F. Parsons [d], Mariella Pattarozzi [a,*], Fabrizio Roncaglia [a,*], Domenico Spinelli [e]

[a] *Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41125 Modena, Italy*
[b] *Dipartimento di Scienze Chimiche e Farmaceutiche, Università degli Studi di Trieste, Via L.Giorgeri 1, I-34127 Trieste, Italy*
[c] *Dipartimento di STEMBIO, Università degli Studi di Palermo, Viale delle Scienze-Parco D'Orleans II, I-90128 Palermo, Italy*
[d] *Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[e] *Dipartimento di Chimica "G. Ciamician", Università degli Studi di Bologna, Via Selmi 2, I-40126 Bologna, Italy*

ARTICLE INFO

Article history:
Received 6 March 2012
Received in revised form 20 April 2012
Accepted 26 April 2012
Available online 8 May 2012

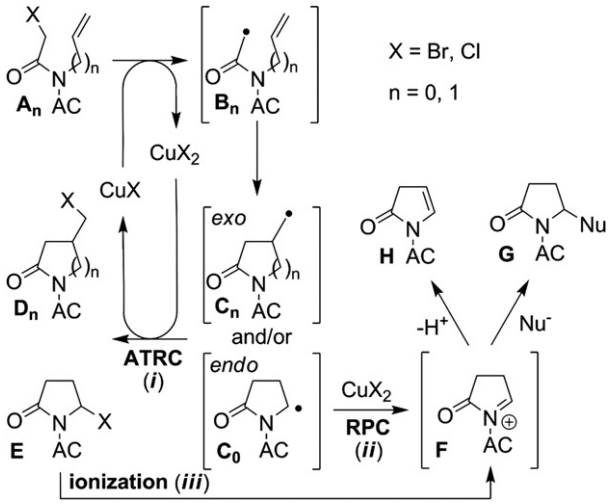
Keywords:
Cyclic ketene-*N*,*S*-acetals
α-Perchloroenamides
Copper(I) chloride
5-*endo* Radical cyclization
Maleic anhydrides

ABSTRACT

The copper-catalyzed radical cyclization (RC) of *N*-α-perchloroacyl cyclic ketene-*N*,X(X=O, *N*R, *S*)-acetals was studied. While the RC of *N*-acyl ketene-*N*,*O*-acetals was unsuccessful, the 5-*endo* cyclization of the other ketene acetals provided much better results, with the following order of cyclization efficiency: hexa-atomic cyclic ketene-*N*,*N*R-acetals<penta-atomic cyclic ketene-*N*,*S*-acetals<hexa-atomic cyclic ketene-*N*,*S*-acetals. Invariably the catalytic cycle begins with the formation of a carbamoyl methyl radical. This leads to a cascade of reactions, including a radical polar crossover step, which ends with the formation of the maleimide nucleus, or precursors of this. Products from the RC of the hexa-atomic cyclic ketene-*N*,*S*-acetals, were efficiently transformed into disubstituted maleic anhydrides.

1. Introduction

The 5-*exo*- or 5-*endo*-*trig* cyclization of *N*-allyl (**B**$_1$) or *N*-vinyl (**B**$_0$) carbamoyl methyl radicals is a valuable tool for the construction of γ-lactams (Scheme 1).[1] However, for *N*-vinyl radicals **B**$_0$, the regioselectivity of the cyclization can change and afford also β-lactams, through an alternative 4-*exo*-*trig* attack, which, according to Baldwin's rules,[2] should be favored. Yet in many cases, the 5-*endo* radical cyclization (RC) is followed, yielding the five-membered ring as the main, or the sole product.[3] Now it is ascertained that the course of the reaction is strongly influenced by the stability of the cyclic radical intermediates **C**$_0$.[3,4] Although the *exo*-**C**$_0$ adduct is kinetically favored,[5] in the absence of adjacent radical stabilizing groups (i.e., Ph, SR) it is converted, through the carbamoyl methyl radicals **B**$_0$, into the more stable *endo*-**C**$_0$ adduct.[6] In any case, a substituent on the amide nitrogen, acting as a cyclization auxiliary (AC), is required to force the molecule to adopt a conformation, whereby the radical center is positioned in close proximity to the radicophile.[7]



Scheme 1. Cu(I)-catalyzed radical cyclization of *N*-allyl (*n*=1) and *N*-vinyl (*n*=0) α-halo-amides (AC=cyclization auxiliary).

By far the most common method of preparing radicals **B** is by homolytic cleavage of the C$_\alpha$-halogen bond in *N*-allyl- or *N*-vinyl-α-halo-amides **A**$_n$ with Bu_3SnH, in the presence of a radical

* Corresponding authors. Tel.: +39 059 2055049; fax: +39 059 373543; e-mail address: franco.ghelfi@unimore.it (F. Ghelfi).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.04.117

initiator.[3a,4b,6,8] This methodology has been, nowadays, surpassed by the atom transfer radical cyclization (ATRC), promoted by transition metals, usually Cu(I)X complexes with polydentate nitrogen ligands.[1c,3b,4a,7,9] In these reactions, the amide radicals $\mathbf{B}_n$, delivered through halogen abstraction by the cuprous complex, add to the tethered C=C bond generating the cyclic radicals *exo*-$\mathbf{C}_n$ and/or *endo*-$\mathbf{C}_0$, which react further with the redox catalyst in its oxidized state, returning it to the active reduced form. Practically, these radicals undergo an irreversible halogen atom transfer from the $Cu(II)X_2$ complex with formation of the corresponding fully halogenated products **D** and **E** (Scheme 1, path *i*). However, the α-amido radical *endo*-$\mathbf{C}_0$, from the 5-*endo* cyclization of *N*-vinyl-α-halo-amides, can react by an alternative pathway, involving a radical polar crossover mechanism (RPC) (Scheme 1, path *ii*),[10] due to its tendency to undergo facile oxidation to the acyliminium ion **F**, through a single electron transfer to $Cu(II)X_2$.[11] In this case, a nucleophile can be inserted at the C-5 site, through a process akin to the second step of an S_N1 mechanism (product **G**), or, if a β-hydrogen is present, the reaction can proceed by an E1-type mechanism affording an unsaturated γ-lactam (**H**). For sake of completeness, we cannot omit that the cation **F** can also be formed from the ionization of the chloro-lactams **E** (Scheme 1, path *iii*).[4a,12]

The TMC-ATRC of *N*-vinyl-α-halo-amides[4a,11a–c,12b] is catalytically less efficient than the analogous reaction with *N*-allyl-α-halo-amides,[7,13] and requires larger amounts of the Cu(I) complex, typically 30–100% against 5–10%. We are strongly convinced, that this discrepancy is a consequence of the release of HCl in the reaction medium, during the formation of product **H**.

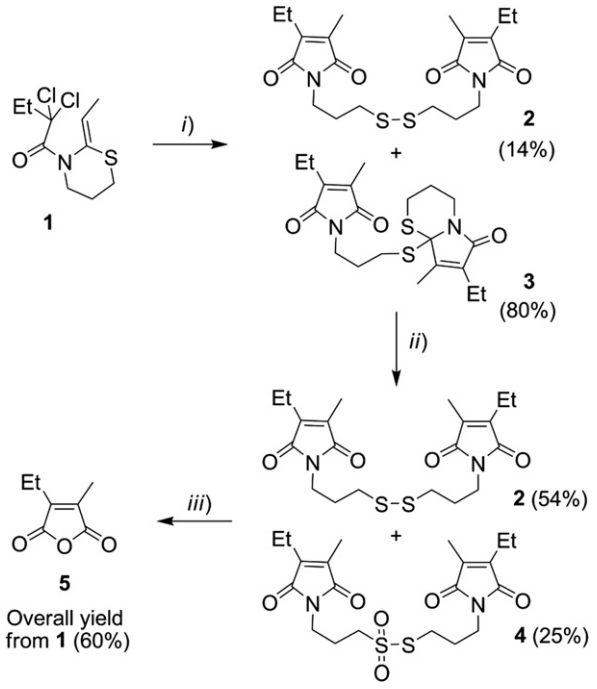
In our group, the Cu(I)-catalyzed ATRC of *N*-allyl-α-perchloro-amides has been extensively studied and used, along with the CH_3ONa mediated functional rearrangement (FR) of the resulting chloro-lactams,[14] to prepare the 3,4-dialkyl-substituted maleic anhydride nuclei,[15] typical frameworks of valuable natural or synthetic products.[16] Since the FR is only viable for the cis-diastereomer and the stereoselectivity of the ATRC cannot be exactly controlled,[7] the formation of the unwanted trans-isomer leads to a loss of efficiency, which can limit the scope of the method.[15a]

Recently, as part of a programme to develop a more versatile route toward chaetomellic anhydrides and their homologs, we reported the preparation of 3-ethyl-4-methylmaleic anhydride **5** through the Cu(I)-catalyzed radical cyclization of the *N*-α-perchloroacyl cyclic ketene-*N*,*S*-acetals **1** (Scheme 2).[17]

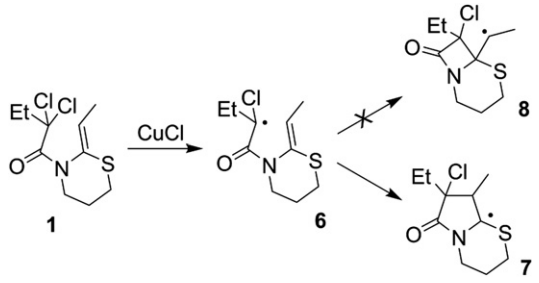
Notwithstanding the first review about ketene acetals was written by McElvain back in 1949,[18] the most comprehensive investigation of the reactivity of these molecules has been provided only in the last 15 years, in particular by the work of the Pittman Jr.'s research group.[19] As far as we are aware, just three examples of RC of *N*-acyl ketene-*N*,X-acetals, two cyclic[19g,20a,b], and one acyclic,[20c] were described before our work, but all three of them concerned the 6-*endo*-*trig* cyclization of β-amide radicals.

Interestingly, in the RC of the cyclic ketene acetal **1** the cyclization auxiliary is already included into the structure. Moreover, the formation of a five-membered ring was exclusive. This is due to the greater stability of the radical intermediate **7** compared to **8** (Scheme 3); the semi-occupied orbital of **7** is stabilized by the adjacent nitrogen and sulfur substituents.

Most likely, products **2** and **3** (Scheme 2) arose from oxidation of the cyclic radical **7**, followed by a cascade of ionic transformations. The addition of carbonate to the reaction mixture was essential to preserve the effectiveness of the redox catalyst. In fact the process releases HCl into the reaction mixture, an event, which is known to disrupt the redox cycle.[21] The RC of the 3-(2,2-dichlorobutanoyl)-2-ethylidenethiazolidine, a *N*-α-perchloroacyl cyclic ketene-*N*,*S*-acetal where the heteroatoms N and S are part of a pentatomic cycle, was also tried. But, compared to **1**, it was more unstable and afforded a more complex reaction mixture, from which the products



Scheme 2. Preparation of the 3-ethyl-2-methyl maleic anhydride **5**: (i) CuCl (10 mol %), TMEDA (20 mol %), MeCN, Na_2CO_3, 17 h, 30 °C; (ii) silica/sulfuric acid, $NaNO_3$, SiO_2/H_2O 3:2, CH_2Cl_2, 40 °C, 17 h; (iii) H_2SO_4/AcOH 1:1, 140 °C, 65 h.



Scheme 3. Regioselective RC of the α-enamide radical **6**.

analogous to **2** and **3** were isolated in a lower yield.[17] Finally, the dimer maleimides **2** and **3** were transformed, as described in Scheme 2, into the desired 3-ethyl-4-methylmaleic anhydride **5**.[17]

The RC of **1** is a clear and effective example of a cascade reaction, involving a radical polar crossover,[22] which represents a novel way to prepare 3,4-dialkyl-substituted maleic anhydrides.

Following this promising result we decided to investigate the reactivity of the *N*-α-perchloroacyl cyclic ketene-*N*,X-acetals **9**–**10** (Fig. 1), wherein S is replaced by the heteroatoms O or N. If the new substrates could give better or analogous performances than those

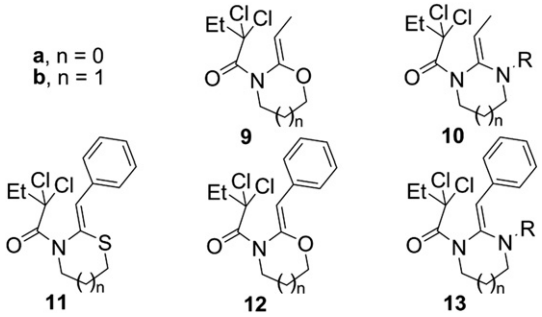


Fig. 1. Archetypal *N*-2,2-dichlorobutanoyl cyclic ketene-*N*,X-acetals.

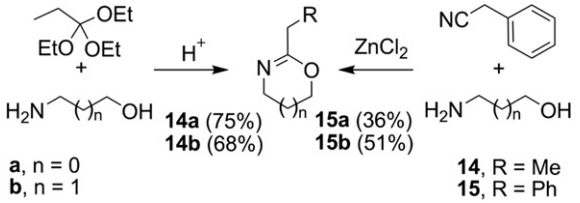
observed with **1**, the use of malodorous sulfurated reagents could be avoided. The ketene-*N*,X-acetals **11**–**13** (Fig. 1) were also taken into account to verify if aromatic substrates could be suitable for the RC process, a crucial step toward the synthesis of the important diaryl maleic anhydrides.[16] All the ketene-*N*,X-acetals **9**–**13** were prepared both with five-membered (a) and six-membered (b) rings. In this article we report the results of our study.

2. Results and discussion

2.1. Preparation of substrates 9–13

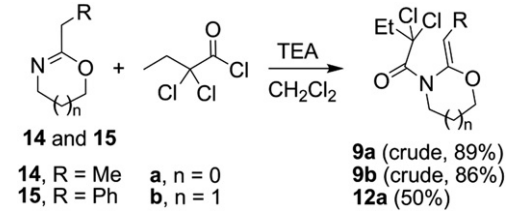
The procedure we considered for the preparation of the enamides **9**–**13**, as used by Pitmann Jr.,[19,20a] involved the acylation of the corresponding imidates, amidines, or thioimidates.[20b–d,23]

2.1.1. Preparation of ketene-N,O-acetals ***9*** *and* ***12****.* 2-Ethyl-4,5-dihydrooxazole (**14a**) and 2-ethyl-5,6-dihydro-4*H*-1,3-oxazine (**14b**) (Scheme 4) were prepared, in good yields, using the reaction between triethyl orthopropionate and the appropriate aminoalcohol, in the presence of acetic acid at 105 °C.[24] 2-Phenylmethyl-4,5-dihydrooxazole (**15a**) and 2-phenylmethyl-5,6-dihydro-4*H*-1,3-oxazine (**15b**) were instead secured in satisfactory yields, starting from phenylacetonitrile (Scheme 4). The best results were achieved, when the condensation of 3-aminopropanol, or 2-aminoethanol, and phenylacetonitrile was performed at 130 °C in chlorobenzene, under the catalytic action of anhydrous $ZnCl_2$ (1–5 mol %) (working under solvent free conditions, we had problems to isolate **15**).[25]



Scheme 4. Preparation of the oxazolines **14** and dihydro-1,3-oxazine **15**.

Cyclic imidates **14** and **15** were then *N*-acylated with 2,2-dichlorobutanoyl chloride to afford the ketene-*N*,*O*-acetals **9** and **12a** (Scheme 5). The reaction must be run under rigorously anhydrous condition and at room temperature. This was required, because products **9** and **12a**, differently from the corresponding ketene-*N*,*S*-acetals are extremely responsive to acid hydrolysis. Indeed **9** cannot be purified by chromatography and, thus, was used as such in the RC tests. This was instead possible with the enamide **12a**, which was isolated, in satisfactory yield, as a mixture with a little amount of hydrolyzed adduct (84:16). Unfortunately **12b** was so unstable that we were unable to recover it, even as a crude product. The configuration of **12a**, assessed by X-ray crystallography, was *Z* (Fig. 2a); we believe that compounds **9** also have the same stereochemistry.



Scheme 5. Preparation of the *N*-2,2-dichlorobutanoyl ketene-*N*,*O*-acetals **9** and **12a**.

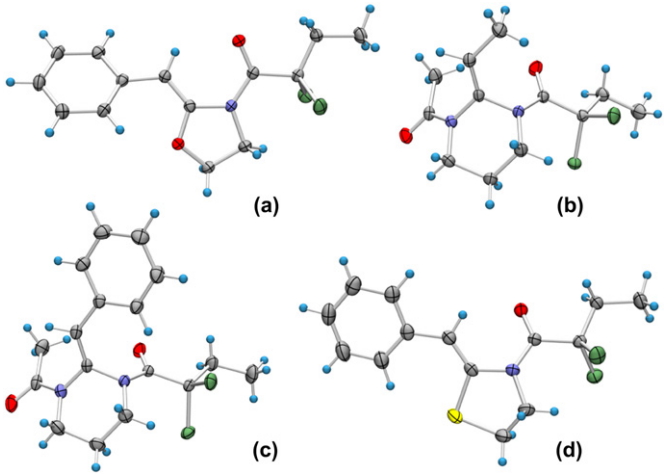


Fig. 2. Molecular structure of compounds **12a** (a), major isomer Ac-**10b** (b), major isomer **13b** (c), and **11a** (polymorph **I**) (d) from X-ray crystallography. Displacement ellipsoids are drawn at 50% probability level. Color code: C=gray, H=light blue, Cl=green, N=blue, O=red, S=yellow.

2.1.2. Preparation of ketene-N,N-acetals. The preparation of the α,α-dichloro-enamides **10** and **13** requires one more step than the synthesis of the corresponding ketene-*N*,X(X=*S*, *O*)-acetals, namely the protection of the secondary nitrogen atom in the cyclic amidines **16** and **17** (Fig. 3) before acylation. In this way, we can prevent the generation of unwanted bis-acylated adducts.

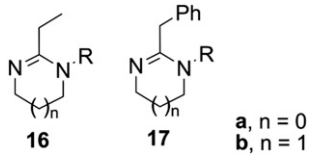


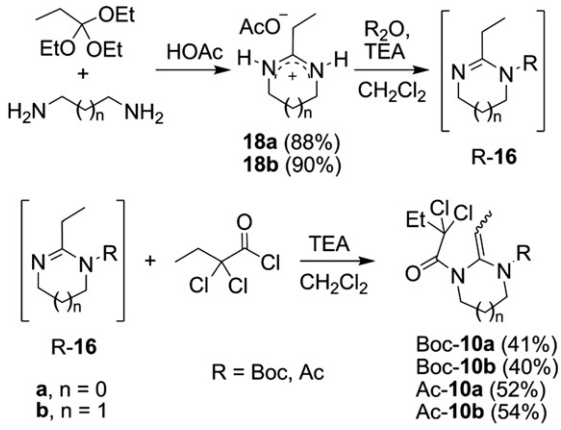
Fig. 3. Cyclic amidines.

Unfortunately, the alkyl substitution proved unsuitable, since the corresponding amidines, on acylation, resulted in polymerization, as a consequence of the high nucleophilicity of the vinylic C_β carbon. Thus we thought to use an electron-withdrawing substituent, such as the *tert*-butyloxycarbonyl (Boc) or acetyl (Ac) group, to reduce the nitrogen nucleophilicity.[19f]

The starting amidines H-**16** were isolated as acetates **18** in high yield, by reacting triethyl orthopropionate and the appropriate diamine, under acid catalysis (Scheme 6).[26] Then, the acylation[27] of **18** with Ac_2O or Boc_2O in anhydrous CH_2Cl_2, using a slight excess of TEA, gave the adducts R-**16**, which, being somewhat unstable (but relatively pure by ^1H NMR), were not purified and used as such. In the next step R-**16**s were smoothly *N*-acylated, under anhydrous conditions, by 2,2-dichlorobutanoyl chloride, affording the expected enamides R-**10** in adequate yields (Scheme 6).

The cyclic ketene-*N*,*NR*-acetals **10**, particularly those with an hexa-atomic ring, were more resistant to hydrolysis than the corresponding ketene-*N*,*O*-acetals **9**, and were purified by silica gel chromatography. In fact Boc-**10a** and Ac-**10a** were isolated as inseparable mixtures together with a small amount of the respective hydrolyzed adducts (for Boc-**10a** the ratio was 88:12 and for Ac-**10a** it was 78:22). However, we were able to recover clean Boc-**10a**, working with chromatographed Boc-**16a**. Interestingly, the hydrolytic byproduct never accompanied the isolation of products derived from R-**10b**s.

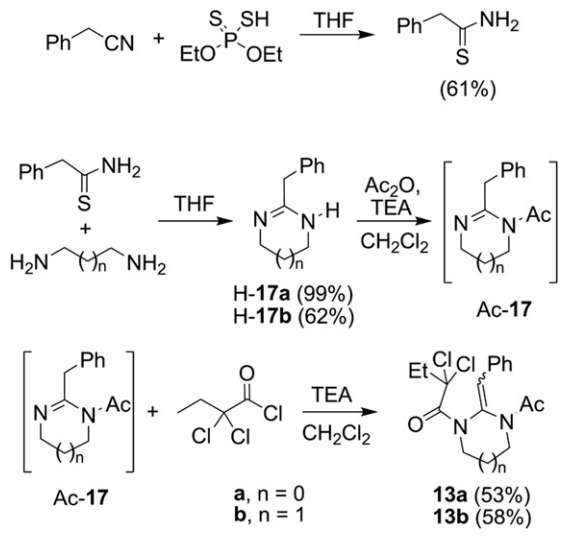
The *N*-α,α-dichloroacyl-ketene-*N*,*S*- or *N*,*O*-acetals **9b**, **11a**–**b**, and **12a** were obtained as single isomers with *Z* configuration. As



Scheme 6. Preparation of the *N*-2,2-dichlorobutanoyl ketene-*N*,*NR*-acetals **10**.

suggested by the broadening of the ^{1}H NMR signals, **9b** and **11b** are made up of a mixture of rotamers. In contrast, the enamides **10** were always isolated as mixtures of geometric isomers *E*/*Z*, each containing a mixture of amide rotamers. The ^{1}H NMR spectrum of product Ac-**10a** shows four sets of signals, which correspond to the two *E*/*Z* isomers each one splitting into two amidic rotamers. On the contrary, the ^{1}H NMR spectra of the other three amides **10** show one set of signals for each diastereomer, albeit broadened due to the presence of rotamers. It was also possible to establish the diastereomeric ratio for Boc-**10a** (74:26 or 91:9, when it was prepared from chromatographed Boc-**16a**), for Boc-**10b** (60:40), and for Ac-**10b** (64:36). The *Z* isomer (the major) of Ac-**10b** was found to crystallize out of the mixture from CH_2Cl_2/hexane at 4 °C and its structure was unambiguously determined by X-ray crystallography, which showed that the 1,3-diazinane ring adopts a chair conformation (Fig. 2b).

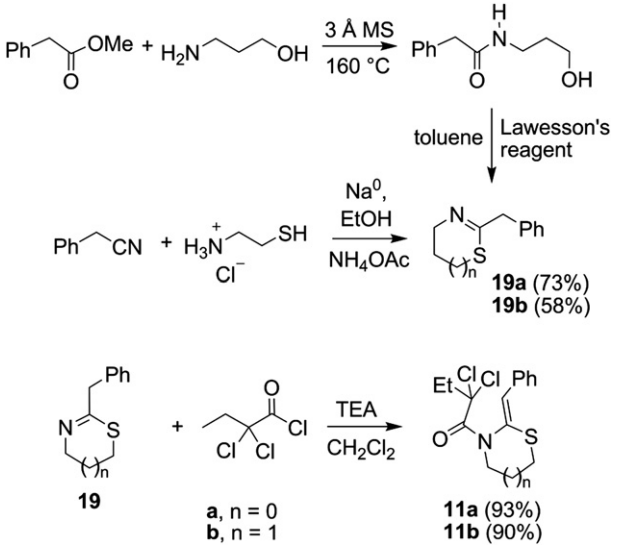
The benzyl amidines H-**17**, on route to the ketene-*N*,*N*-acetals **13**, were obtained by reaction of 2-phenylthioacetamide (synthesized from phenylacetonitrile, adapting the procedure of Shabana)[28] with 1,2-diaminoethane or 1,3-diaminopropane (Scheme 7).[29] For these compounds we considered only the acetylation reaction to protect the secondary nitrogen. The acylation was accomplished with acetic anhydride, as previously described for H-**16**. The resulting amidines Ac-**17**, without purification, were reacted with 2,2-dichlorobutanoyl chloride, providing **13** in satisfactory yields (Scheme 7). Enamides **13** were quite resistant to acid-catalyzed hydrolysis, and so could be



Scheme 7. Synthesis of the *N*-2,2-dichlorobutanoyl ketene-*N*,*NA*c-acetals **13**.

purified by chromatography on silica. Whereas, **13b** contained two separable *Z*/*E* diastereomers (ratio 61:39), **13a** exhibited only a single configuration. As indicated by ^{1}H NMR signal broadening, products **13** are also mixtures of amide rotamers at room temperature. X-ray crystallography assessed the *Z* configuration for the major isomer of **13b**, revealing also a chair conformation for the 1,3-diazinane ring (Fig. 2c).

2.1.3. Preparation of ketene-N,S-acetals. 2-Phenylmethyl-4,5-dihydrothiazole (**19a**) and 2-phenylmethyl-5,6-dihydro-4*H*-1,3-thiazine (**19b**), precursors of enamides **11a** and **11b**, respectively, were secured using the same literature procedure as we followed for preparing the methyl analogs **1** (Scheme 8).[30] X-ray crystallography assessed a *Z* configuration for **11a** (Fig. 2d), which we also expected for compound **11b**.



Scheme 8. Synthesis of the *N*-2,2-dichlorobutanoyl ketene-*N*,*S*-acetals **11**.

The cyclic thioamide **19a** was obtained from the reaction of phenylacetonitrile with cysteamine hydrochloride. In contrast, **19b** was secured through a two-step process: (i) preparation of *N*-(3-hydroxypropyl)-phenylacetamide, from methyl phenylacetate and 3-aminopropanol and (ii) cyclization of the acetamide in the presence of the Lawesson's reagent.

The cyclic thioamides **19** were then smoothly acylated using 2,2-dichlorobutanoyl chloride under anhydrous conditions, to afford the expected ketene-*N*,*S*-acetals **11**, which, being stable to acid-catalyzed hydrolysis, were purified by chromatography on silica (Scheme 8). They were isolated as a single *Z* diastereomer.

2.2. Radical cyclization of substrates 9–13

All the ketene-*N*,X-acetals **9**–**13** were generally reacted under the best experimental conditions observed for the cyclization of **1**: namely, reaction of the substrate (2 mmol), CuCl (10–30 mol %), ligand TMEDA or PMDETA, and K_2CO_3 or Na_2CO_3 (2 mmol), in anhydrous CH_3CN (3 mL), at 30 °C for 16 h.[17]

*2.2.1. Radical cyclization of ketene-N,O-acetals **9** and **12a**.* Ketene-*N*,*O*-acetals **9** and **12a**, despite the several trials, gave no cyclic products. Uniquely, under the reaction conditions, they were found to hydrolyse to give the respective ester-amides.

*2.2.2. Radical cyclization of ketene-N,NR-acetals R-**10** and **13**.* The RC of the penta-atomic *N*-2,2-dichloroacyl-ketene-*N*,*NR*-acetals R-

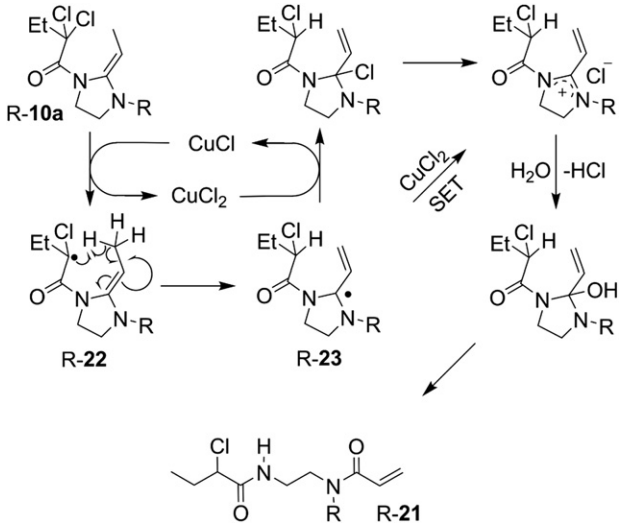
10a and **13a**, gave variable results, as a function of the substituent (Me or Ph) on the C=C bond, whereas the protecting group R showed a minor impact on the results (Table 1).

Table 1
RC of *N*-2,2-diCl-butanoyl ketene-*N*,*NR*-acetals R-**10a** and **13a**[a]

No.	Substrate	Conv.[c] (%)	R-**20a**[b,c] (%)	R-**21**[c] (%)	(±)-**24**[c] (%)
1	Boc-**10a** (dr 91:9)	97	11	49	—
2	Ac-**10a**[d]	100	30	10	—
3	**13a**	100	—	—	72(97)[e]

[a] Reaction conditions: substrate (2 mmol), CuCl (30 mol %), PMDETA (33 mol %), K_2CO_3 (2 mmol), anhydrous CH_3CN (3 mL), 30 °C, 16 h.
[b] *N*-(2-(*NR*-Propionamido)ethyl)-2,2-dichlorobutanamide (R=Ac or Boc).
[c] Determined on isolated material.
[d] This substrate (a mixture of rotamers of *E*/*Z* diastereomers) was used together with Ac-**20a** (78:22).
[e] In parentheses, the product yield under the following conditions: CuCl (5 mol %), TMEDA (10 mol %), Na_2CO_3 (2 mmol).

Enamides R-**10a** afforded complex reaction mixtures, where the main products were R-**20a** (from substrate hydrolysis) and the mono-chloro butanamide R-**21**. A possible rationalization for the formation of R-**21** is outlined in Scheme 9. The reaction between R-**10a** and the Cu(I) complex generates the initial carbamoyl methyl radical R-**22**, which, instead of cyclising, abstracts a hydrogen atom from the terminal methyl group, forming a resonance-stabilized allylic radical intermediate R-**23** (the resonance form shown below is also stabilised by two adjacent acylamino groups). At this point the reaction can follow one or both of the two pathways, we have previously described in Scheme 1, yielding an intermediate acyliminium cation, which, after reaction with H_2O, is transformed into the mono-chloro diamide R-**21**.



Scheme 9. A plausible mechanism for the formation of R-**21**.

Formation of R-**23** by this mechanism is only possible if, in R-**10a**, the methyl appendage, bound to the C_β vinylic site, is in close proximity to the 2,2-dichlorobutanoyl group. Taking into account the starting dr of Boc-**10a** and the significant yield of Boc-**21**, we can confidently attribute the *Z* configuration to the major diastereomer of Boc-**10a** (giving highest priority to the halogenated substituent); the same should be true for Ac-**10a**.

Differently, the enamide **13a**, under the same reaction conditions, gave exclusively the tetracyclic epoxy-azepinone **24** (Fig. 4) in a respectable 72% yield, which even rose to 97%, using 5 mol % of CuCl/[TMEDA]$_2$ and Na_2CO_3, as base.

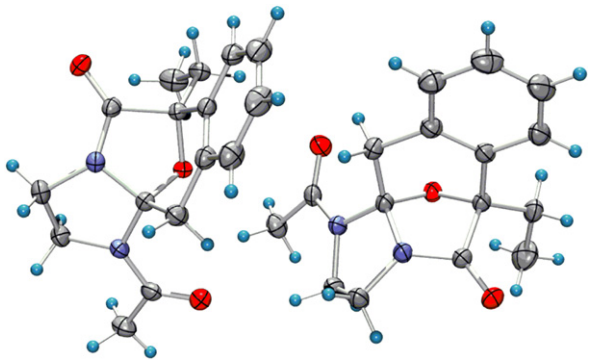
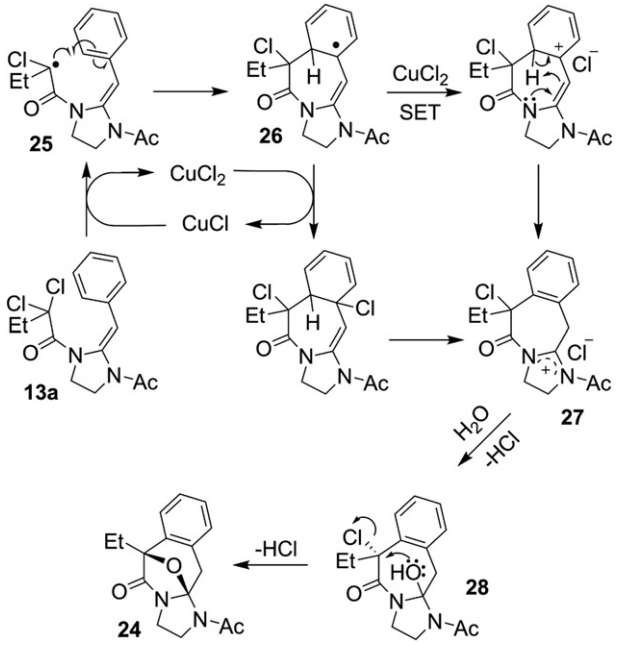


Fig. 4. Structures of the two crystallographically independent molecules in compound **24** from X-ray crystallography. Displacement ellipsoids are drawn at 30% probability level. Same color code as in Fig. 2.

X-ray quality crystals of **24** were grown by slow evaporation of CH_2Cl_2/*n*-hexane solutions and structure determination was carried out by X-ray crystallography. The crystal comprises two crystallographically independent molecules with virtually identical geometry, shown in Fig. 4. The two asymmetric carbons (C2 and C5 in the oxazolidine-4-one moiety) are found to have opposite absolute configurations. However, the compound crystallizes in centrosymmetric space group $P2_1/c$ and the crystal is a racemic mixture of the (*R*,*S*) and (*S*,*R*) enantiomers (Fig. 4).

We presume that the preparation of **24** from **13a** starts with the formation of the carbamoyl methyl radical **25** (Scheme 10). This radical cyclizes onto the aromatic ring forming the seven-membered cyclic radical intermediate **26**, which, analogously to the radical adduct **23** (Scheme 9), is converted into the acylimminium cation **27**. This transformation is assisted by restoring the aromaticity of the phenyl group and by the formation of a resonance-stabilized carbocation. The acyliminium cation **27** is then quenched by H_2O affording the adducts **28**. In this case, however, an acyclic diamide is not formed (Scheme 9); on the contrary, **28** is converted into **24**, through an intramolecular nucleophilic substitution reaction of the hydroxyl group with the C_α–Cl bond. Since the substitution is of S_N2 type, the entering *O*-nucleophile and the

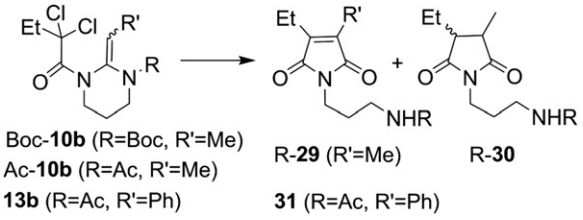


Scheme 10. A plausible mechanism for the formation of **24**.

outgoing halide must adopt an *anti*-periplanar configuration. It is certainly interesting to clear how this occurs, but currently it is outside the scope of this study (besides we cannot exclude the alternative/parallel mechanism where the hydrolysis of the C–Cl α to C=O bond precedes the formation of the acyliminium ion). As for enamides R-**10a**, a *Z* configuration of the C=C bond of **13a** is required for successful transformation into **24**; so, we can reasonably assign the *Z* configuration to the starting enamide **13a**.

In the literature, the intramolecular Friedel–Crafts alkylation of *N*-biphenyl-2-chloroacetamides, molecules that are structurally analogous to **13a**, gave dibenzoazepinones, condensed hepta-atomic ring systems, which were used for the preparation of γ-secretase inhibitors (for application in the treatment of the Alzheimer's disease).[31] As far we are aware, the efficient transformation of **13a** into (±)-**24** is the first example of a 7-ring forming copper-catalyzed radical cyclization of *N*-styryl-α-perchloroamides.

The performances of the RC of the six-membered ring *N*-α,α-dichloroacyl-ketene-*N*,*N*R-acetals R-**10b** and **13b** were, on the contrary, less influenced by the Me or Ph substituents on the vinylic group (Scheme 11 and Table 2). With R-**10b**—where a methyl is bound to the vinylic component—we isolated two main products: the maleimide R-**29** and the succinimide R-**30**, the latter as a mixture of cis/trans diastereomers. The product yields are not influenced by changing the R protection on the nitrogen atom (Table 2, No. 1 and 3). However the conversion of Boc-**10b**, when using 30 mol % of CuCl, was almost complete, whereas that of Ac-**10b** showed partial (79%). In this case, the unreacted Ac-**10b** (21%) was recovered as the pure *Z* diastereomer. Interestingly, there was no evidence that the geometric configuration of the C=C bonds in **10b**s had any impact on the products obtained.



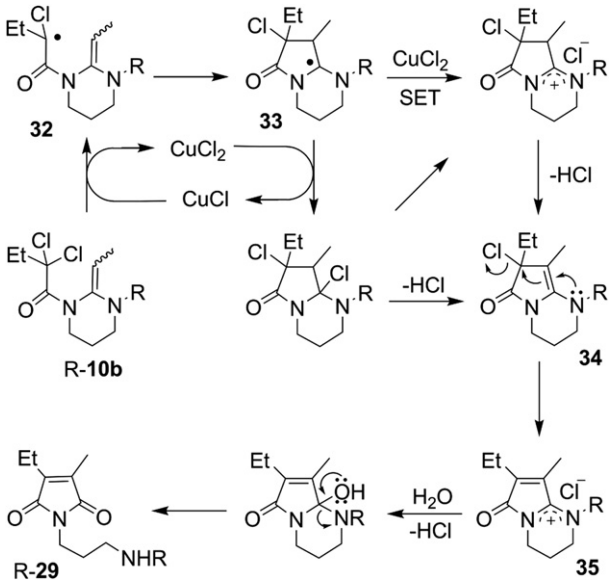
Scheme 11. RC of *N*-2,2-diCl-butanoyl ketene-*N*,*N*R-acetals R-**10b** and **13b**.

Table 2
RC of *N*-2,2-diCl-butanoyl ketene-*N*,*N*R-acetals R-**10b** and **13b**[a]

No.	Substrate	Conv.[b] (%)	R-**29** or **31**[b] (%)	R-**30**[b] (%)
1	Boc-**10b** (dr 60:40)	96	57	13 (dr 74:26)
2[c]	Boc-**10b** (dr 60:40)	22	8	—
3	Ac-**10b** (*Z*/*E* 64:36)	79	56	7 (dr 86:14)
4	**13b** (*Z*/*E* 57:43)	100	59	—
5	**13b** (*Z*/*E* 100:0)	100	72	—
6	**13b** (*Z*/*E* 0:100)	100	46	—

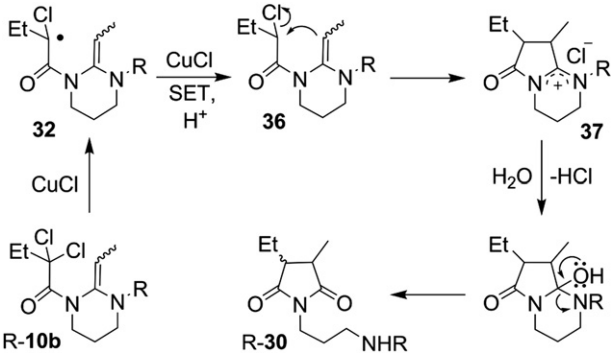
[a] Reaction conditions: substrate (2 mmol), CuCl (30 mol %), PMDETA (33 mol %), K_2CO_3 (2 mmol), anhydrous CH_3CN (3 mL), 30 °C, 16 h.
[b] Determined on isolated material.
[c] CuCl (10 mol %), TMEDA (20 mol %), Na_2CO_3 (2 mmol).

The maleimide nucleus is likely to be formed according to the mechanism outlined in Scheme 12. As usual, the catalytic cycle begins with the formation of the carbamoyl methyl radical **32**, which cyclizes following the expected 5-*endo* mechanism. The formation of the cyclic radical intermediate **33**, as previously discussed, can proceed through a classic ATRC and/or via a RPC pathway. Deprotonation gives intermediate **34**, the precursor of the allylic acyliminium cation **35**, which, after quenching with H_2O and ensuing elimination, is transformed into the maleimide R-**29**.



Scheme 12. A plausible mechanism for the formation of the maleimide R-**29**.

Since R-**29**, under the same conditions of the RC reaction, did not give the succinimide R-**30**, the latter should derive directly from the substrate R-**10b**, most likely through the mechanism drawn in Scheme 13. This process implies that the initial reduction of the starting *N*-α,α-dichloroacyl-ketene-*N*,*N*R-acetal R-**10b** gives the α-mono-chloroamide **36**. Then, substitution of the highly electrophilic C_α–Cl carbon, by the nucleophilic end of the ketene-*N*,*N*-acetal segment, affords the cyclic acyliminium cation intermediate **37**. The transformation concludes with a hydrolytic mechanism, common to the other cases examined, to give R-**30**.



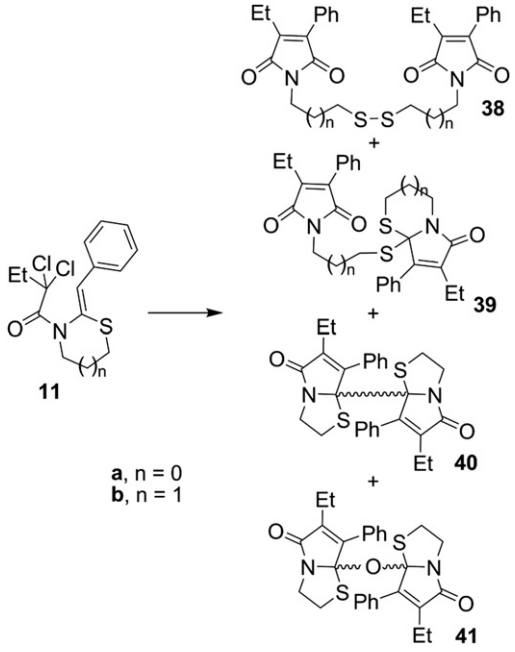
Scheme 13. Possible mechanism for the formation of the succinimide R-**30**.

The aromatic substrate **13b**, instead, gave exclusively the maleimide product **31** (the mechanism of the process is the same as the one outlined in Scheme 12). The yield of **31** was higher when starting from the *Z* diastereomer than from the *E* isomer (Table 2, nos. 5 and 6), although the reason for this is unknown.

On comparing the results obtained with the pent- and hexa-atomic cyclic ketene-*N*,*N*R-acetals, we can note that the radical 5-*endo* cyclization was only possible for precursors containing the larger rings (**b**). This might be a consequence of a closer proximity of the radical center and radicophilic C=C in these precursors, or most likely it is the greater flexibility of the larger ring that can allow the reacting group to come together.

*2.2.3. Radical cyclization of ketene-N,S-acetals **11**.* Reaction of the thioenamide **11a**, under typical conditions, afforded a complex reaction mixture, wherefrom related products, to those we observed

in our seminal study of the RC of 3-(2,2-dichlorobutanoyl)-2-ethylidenethiazolidine,[17] were isolated: namely, the disulfide dimer **38a**, the sulfide dimer **39a**, and the C–C dimer *dl*-**40** (Scheme 14 and Table 3). In addition, two other unisolable products were detected, to which we assigned the structure *meso*-**40** and **41** (their yields, determined by ^{1}H NMR, were always less than 10%).



Scheme 14. RC of *N*-2,2-diCl-butanoyl ketene-*N*,*S*-acetal **11**.

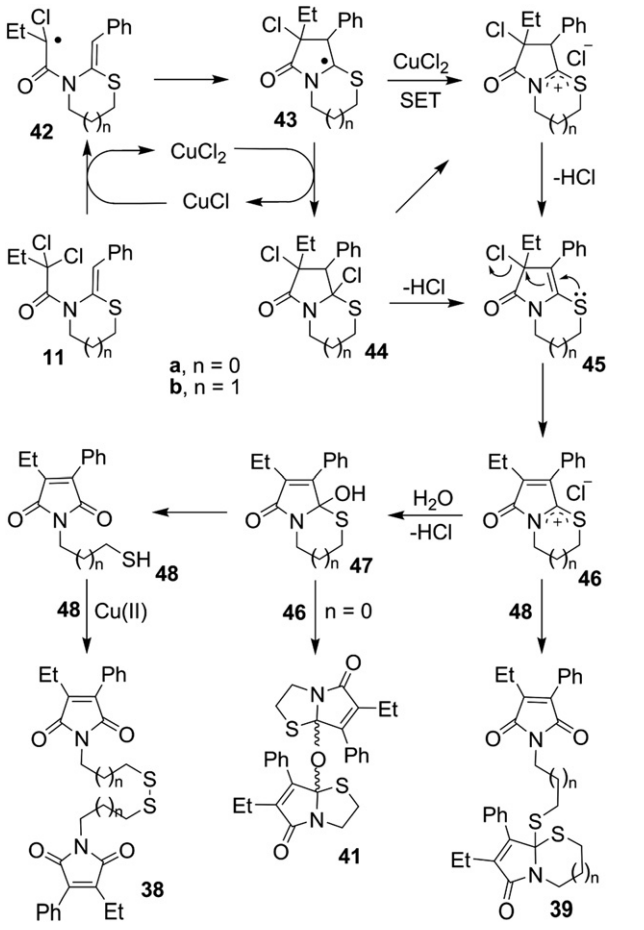
Table 3
RC of *N*-2,2-diCl-butanoyl ketene-*N*,*S*-acetals **11**[a]

No	Sub.	CuCl[L]$_n$[b] (mol %)	Conv.[c] (%)	Products[c,d] (%)				
				38	**39**	*dl*-**40**	*meso*-**40**	**41**
1[e]	**11a**	A (30)	94	29	29	22	8	6
2	**11a**	B (10)	100	26	48	16	5	3
3	**11a**	B (5)	99	16	51	17	6	4
4	**11b**	B (5)	100	23	62	—	—	—

[a] Reaction conditions: substrate (2 mmol), Na_2CO_3 (2 mmol), anhydrous CH_3CN (3 mL), 30 °C, 16–17 h.
[b] A=CuCl[PMDETA], B=CuCl[TMEDA]$_2$.
[c] Determined on isolated material.
[d] Determined by ^{1}H NMR for products **40** and **41**.
[e] K_2CO_3 (2 mmol) was used as base.

Products **38a**, **39a**, and **41**, likely, arise from the tandem radical polar process outlined in Scheme 15, which resembles the one shown in Scheme 12 for the RC of ketene-*N*,*N*R-acetals R-**10b** and **13b**. The process starts with the 5-*endo* radical cyclization of **42a** to give the cyclic radical **43a**. The reaction proceeds with the conversion of **43a** into the transient ketene-*N*,*S*-acetal **45a**, and its subsequent hydrolysis, through the hydroxy adduct **47a**, gives the maleimide **48a**. This adduct can act as an *S*-nucleophile and attack the *N*-acyliminium ion **46a**, derived from **45a**, yielding the sulfide dimer **39a**, or alternatively, on oxidation, afford the disulfide dimer **38a**. The side product **41**, in turn, can be produced by nucleophilic attack of the hydroxy function of **47a** on **46a**.

The C–C dimer **40** might, instead, come from the dehydrochlorination of **49**, a postulated intermediate dimer, derived from homo-coupling of radicals **43a**. Alternatively, it is also possible that the ATRC γ-lactam **44a** loses HCl, and the resulting Δ^2



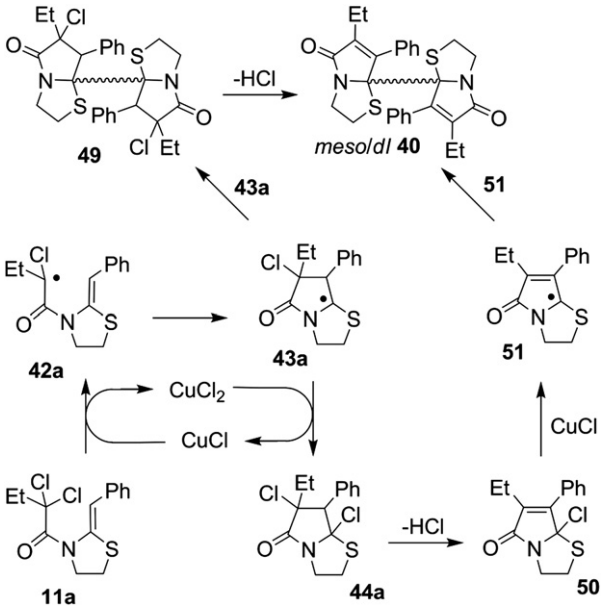
Scheme 15. Possible mechanism for the formation of products **38**, **39**, and **41**.

unsaturated lactam **50** gives dimer **40** through a reductive homo-coupling process (Scheme 16). This last route is supported by literature examples.[32] Indeed, the capability of copper catalysts to promote the reductive radical homo-coupling of allyl halides is well known, and has been exploited to prepare natural compounds such as terpenes, bisantraquinones and butenolides.[33]

The product **40** has two stereogenic centers, but can also have a symmetry plane. All the three possible stereomers of **40** were produced: one achiral (*meso*-**40**) and the other two as racemic mixture (*dl*-**40**).

The *dl* isomer was separated from the *meso*-isomer and from the side product **41** by crystallization from CH_2Cl_2/*n*-hexane. Its structure and configuration were unambiguously determined by X-ray crystallography (Fig. 5). The two asymmetric carbons in the structure were found to have the same absolute configuration. However, since the compound crystallizes in centrosymmetric space group *Pccn*, the crystal is a racemic mixture of (*R*,*R*) and (*S*,*S*) enantiomers. The lattice comprises three crystallographically independent molecules, two of which develop around twofold crystal axes and consequently have rigorous C_2 symmetry. The pseudo-twofold symmetry of the remaining molecule is broken principally by the conformation of the ethyl substituents. The N–C–C–N torsion angle involving the quaternary carbon atoms is close to 180°, taking the values 179.7(2), 176.0(2) and 174.28(13) in the three molecules, respectively.

Being in mind our aim to prepare disubstituted maleic anhydrides, the formation of the dimer **40**, although interesting, constitutes a serious limitation for the RC of the enamide **11a**, as **40** cannot be converted into a maleimide nucleus. Some trials to minimise



Scheme 16. Possible mechanism for the formation of products **40**.

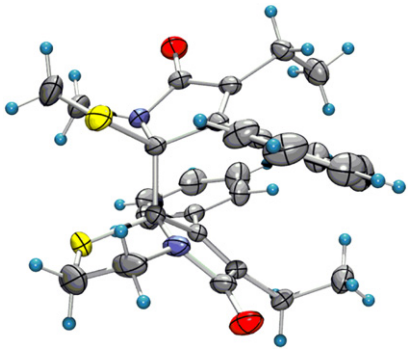


Fig. 5. Structure of one of the three crystallographically independent molecules in compound *dl*-**40** from X-ray crystallography. Displacement ellipsoids are drawn at 30% probability level. Same color code as in Fig. 2.

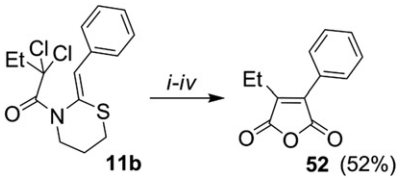
these byproducts were unsuccessful. Thankfully, the RC of the six members cyclic ketene-*N*,*S*-acetal **11b**, similarly to the methyl analogous **1** (Scheme 2), produced more simple reaction mixtures, essentially composed of dimers **38b** and **39b** (Table 3, no. 4).

Replacing the methyl group with phenyl makes the catalytic system more effective and allows efficient conversion with a redox complex charge of only 5 mol % (Table 3, nos. 3 and 4, Scheme 2). It is clear from the results observed with the aromatic *N* or *S* ketene-*N*,X-acetals **13b** (Table 2) or **11b** (Table 3), that the phenyl substituent was unable to direct (even partially) the cyclization toward a 4-*exo*-*trig* mode. Probably, the imperfect overlap between the p orbital of the radical center and the aromatic π system, reduces the stability of an intermediate benzyl radical.[34] As a consequence the 5-*endo*-*trig* cyclization mode, giving an intermediate radical cooperatively stabilized by the acylamino and alkylthio groups, remains favored and it was the only pathway observed.

2.3. Preparation of the 3-ethyl-4-phenylfuran-2,5-dione

The previous experiments identified the six-membered *N*-acyl ketene-*N*,*S*-acetals as being the best starting material for the RC reaction, both because they are easy to prepare, purify and manipulate (they are resistant to hydrolysis), and because their transformations are more selective. Thus, analogously to the previous conversion of the cyclic products of **1** into the 3-ethyl-4-methyl-2,5-furandione **5**, the same transformation was attempted with **38b** and **39b**. We, however, encountered insurmountable problems during the acid hydrolysis of **38**. For this reason we switched to using Argade's two-step hydrolysis protocol, for the conversion of the maleimide nucleus into the corresponding maleic anhydride.[35]

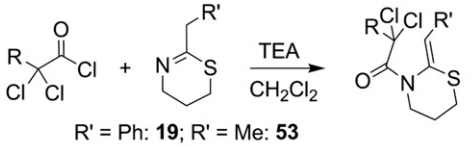
Scheme 17 summarizes the preparation of the maleic anhydride **52** from the enamide **11b**. The *N*-2,2-dichlorobutanoyl ketene-*N*,*S*-acetal **11b** was cyclized in CH_3CN, using the catalyst CuCl/TMEDA. The dimers **38** and **39** were not isolated, but together they were subjected to an oxidative treatment to form the C=O group, masked as an *S*,*S*-acetal in **39**. The crude products from this step were then hydrolyzed according to Argade's method, affording the expected anhydride **52** in a more than acceptable 52% overall yield.



Scheme 17. Preparation of the 3-ethyl-4-phenyl-2,5-furandione **52**: (i) CuCl (5 mol %), TMEDA (10 mol %), MeCN, Na_2CO_3, 17 h, 30 °C; (ii) silica/sulfuric acid, $NaNO_3$, SiO_2/H_2O 3:2, CH_2Cl_2, 45 °C, 40 h; (iii) KOH, CH_3OH/THF, reflux 2 h; (iv) HCl (10%), rt.

2.4. Extension of the method

Next we investigated the change of the acyl group bound to the nitrogen atom of the archetypal 2-ethyliden- or 2-benzyliden-1,3-thiazinane nuclei. All the starting enamides were prepared, in satisfactory yields (63–79%), through the typical reaction between acyl chlorides and 2-ethyl-5,6-dihydro-4*H*-1,3-thiazine **53**[30] or 2-benzyl-5,6-dihydro-4*H*-1,3-thiazine **19** (Scheme 18).



R' = Ph: **19**; R' = Me: **53**

R = $CH(CH_3)_2$, R' = CH_3: **54** (79%)
R = C_6H_5, R' = CH_3: **55** (73%)
R = Cl, R' = CH_3: **56** (63%)
R = C_6H_5, R' = C_6H_5: **57** (73%)

Scheme 18. Preparation of *N*-2,2-dichloroacyl ketene-*N*,*S*-acetals **54**–**57**.

We also tried to synthesize the 3-trichloroacetyl-2-(*Z*)-benzyliden-1,3-thiazinane, but owing to its utmost lability, all attempts to trichloro-acetylate the thiazine **53** were unsuccessful. The dichloroacetyl chloride was, instead, deliberately not prepared, because acyl chlorides with hydrogens on the C_α are generally not efficiently converted into *N*-acyl-ketene-*N*,X-acetals.[23a,36,37]

The structure of enamide **57** was unambiguously determined by X-ray crystallography. This confirmed the expected *Z* configuration (Fig. 6), and this configuration can be safely assigned to the other enamides (**54**–**56**).

Scheme 19 reports the structure of the products isolated from the RC of the ketene-*N*,*S*-acetals **54**–**57**—the expected disulfide (**A**) and sulfide (**B**) dimers—while Table 4 collects the results of all the RC of the 3-(2,2-dichloroacyl)-2-(*Z*)-alkyliden-1,3-thiazinanes. The combined yields of the two dimers were generally good (>85%),

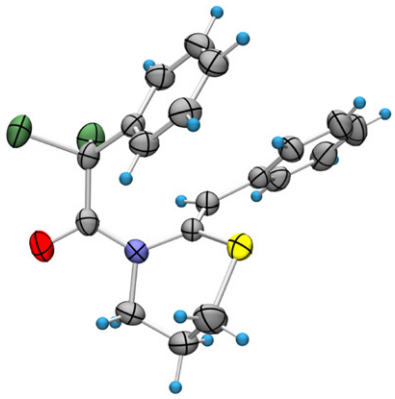
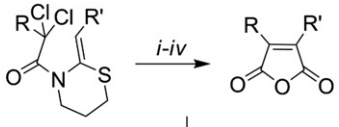


Fig. 6. Molecular structure of compound **57** from X-ray crystallography. Displacement ellipsoids are drawn at 50% probability level. Disorder effects on the carbon atoms of the 1,3-thiazinane ring are omitted for clarity and only the majority conformer is shown. Same colour code as in Fig. 2.

apart the one obtained from the trichloroenamide **56** (<60%; Table 4, item 4). Again it was confirmed that the redox complex charge can be lowered to 5 mol %, when the *N*-α-perchloroacyl-benzyliden-1,3-thiazinanes were reacted (Table 4, nos. 5 and 7).



	enamide	anhydride
R = CH_2CH_3, R' = CH_3	**1**	**3** (60%)
R = $CH(CH_3)_2$, R' = CH_3	**54**	**66** (74%)
R = C_2H_5, R' = C_6H_5	**11b**	**52** (52%)
R = C_6H_5, R' = CH_3	**55**	**67** (65%)
R = Cl, R' = CH_3	**56**	**68** (24%)
R = C_6H_5, R' = C_6H_5	**57**	**69** (75%)

Scheme 19. RC of *N*-2,2-dichloroacyl ketene-*N*,*S*-acetals **54**–**57**.

Table 4
RC of *N*-2,2-diCl-butanoyl ketene-*N*,*S*-acetals[a]

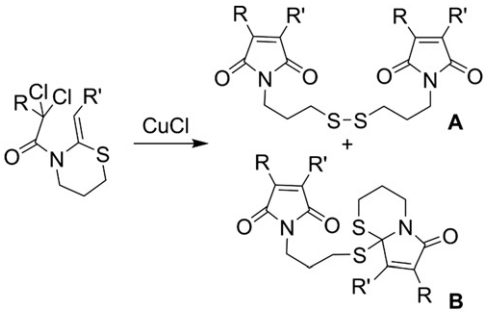
No.	Sub.	CuCl[TMEDA]$_2$ (mol %)	Conv.[b] (%)	Products[b] (%)	
1	**1**	10	100	**2** (14)	**3** (80)
2	**54**	10	100	**58** (19)	**59** (73)
3	**55**	10	100	**60** (15)	**61** (83)
4	**56**	10	100	**62** (26)	**63** (29)
5	**11b**	5	100	**38b** (23)	**39b** (62)
6	**57**	10	100	**64** (45)	**65** (53)
7	**57**	5	100	**64** (7)	**65** (92)

[a] Reaction conditions: substrate (2 mmol), Na_2CO_3 (2 mmol), anhydrous CH_3CN (3 mL), 30 °C, 16–18 h.
[b] Determined on isolated material.

Finally we completed the conversion of the 3-(2,2-dichloroacyl)-2-(*Z*)-alkyliden-1,3-thiazinanes into the corresponding maleic anhydrides, without purifying any intermediates, as outlined in Scheme 20. The desired disubstituted maleic anhydrides were isolated in acceptable global yields (>50%), except for the case of the trichloroacetylenamide **56**, which gave, owing to the less efficient RC, a much reduced global yield of only 24%.

3. Conclusions

In this work we have studied the novel copper-catalyzed ring cyclization (RC) of *N*-α-perchloroacyl cyclic ketene-*N*,X(X=*O*, *NR*, *S*)-acetals, substrates that were prepared by acylation of the corresponding imidates, amidines, or thioimidates.



	enamide	A	B
R = $CH(CH_3)_2$, R' = CH_3	**54**	**58**	**59**
R = C_6H_5, R' = CH_3	**55**	**60**	**61**
R = Cl, R' = CH_3	**56**	**62**	**63**
R = C_6H_5, R' = C_6H_5	**57**	**64**	**65**

Scheme 20. Preparation of the 3,4-disubstituted-2,5-furandiones: (i) CuCl (5 mol %), TMEDA (10 mol %), MeCN, Na_2CO_3, 17 h, 30 °C; (ii) silica/sulfuric acid, $NaNO_3$, SiO_2/H_2O 3:2, CH_2Cl_2, 45 °C, 40 h; (iii) KOH, CH_3OH/THF, reflux 2 h; (iv) HCl (10%), rt. In the case of enamide **1** the datum was gathered from Ref. 17, and the hydrolytic procedure is different.

While the RC of *N*-acyl ketene-*N*,*O*-acetals was unsuccessful, the 5-*endo* cyclization of the other ketene acetals provided better results, with cyclization efficiency in the order: hexa-atomic cyclic ketene-*N*,*NR*-acetals<penta-atomic cyclic ketene-*N*,*S*-acetals<hexa-atomic cyclic ketene-*N*,*S*-acetals. Invariably the catalytic cycle begins with the formation of a carbamoyl methyl radical, which leads to a cascade of reactions, including a radical polar crossover step, culminating in the formation of the maleimide nucleus, or of a direct precursor (that can be transformed into a maleimide by simple hydrolysis). Globally, this is an elegant example of redox economy, in that the starting material of the RC is subjected to a transformation equivalent to a refunctionalization by an internal redox reaction.[38]

The products from the RC of the hexa-atomic cyclic ketene-*N*,*S*-acetals, being secured in higher yields (incidentally the starting enamides are also relatively easy to prepare) were then transformed into maleic anhydrides. This process bypasses the stereoselectivity problem typical of the ATRC-FR method to form maleic anhydrides.[15] The new process is suitable for the synthesis of dialkyl, arylalkyl, or diaryl anhydrides (these last compounds are otherwise inaccessible with the ATRC-FR method).

The penta-atomic *N*-acyl cyclic ketene-*N*,*NR*-acetals were, on the contrary, unsuitable for the 5-*endo* RC. However, when a benzylidene substituent was included at the C-2 position of the imidazolidine nucleus, a remarkable and unprecedented 7-ring RC, involving the aromatic ring, occurred, which produced, in an astonishingly efficient way, the tetracyclic epoxy-azepinone (±)-**24**.

4. Experimental part

4.1. General

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka, or RdH, and generally used without further purification. CH_3CN and CH_2Cl_2 (DCM) were dried over 3 Å sieves (5% w/v). $ZnCl_2$ was dried with trimethylchlorosilane, as reported in literature.[39] Acyl chlorides were prepared by chlorination with Cl_2 of acyl chlorides in the presence of tetrabutylammonium chloride.[40] The 2-ethyl-5,6-dihydro-4*H*-1,3-thiazine **53**[30] and silica–sulfuric acid[41] were secured following

literature procedures. The silica gels used for gravity or flash chromatography were, respectively, Silica Gel 60 Merck 0.063–0.2 mm or 0.040–0.063 mm. TLC was performed on silica coated plates Merck 60 F_{254}, using UV light (254 nm), iodine, and ninhydrin or cerium molybdate solutions to visualize the spots.

^{1}H NMR spectra were recorded on 'Bruker DPX 200', 'Bruker Avance 400' and 'Varian 500 MHz'. ^{13}C NMR was obtained with full proton decoupling. ^{1}H NMR and ^{13}C NMR signals attribution was based on Gradient-Enhanced ^{1}H,^{1}H-DQF-COSY, ^{1}H,^{13}C-Edited-HSQC, and ^{1}H,^{13}C-HMBC experiments, run with standard pulses programmes. IR and MS spectra were recorded, respectively, on a 'FTIR Perkin Elmer 1600 Series' and a 'HP G1800C GCD System Series II' or a 'LCeMS(n) Ion Trap 6310A Agilent Technologies'. High-resolution mass spectra (HRMS) were obtained on a 'Bruker Daltonics microTOF II' or an 'Agilent 6520 Accurate-Mass Q-TOF LC/MS'. Melting point was determined with an 'Electrothermal Series IA9100 Digital Melting Point Apparatus'.

Structural determinations on Ac-**10b** (major diastereomer), **11a**, **12a**, **13b** (major diastereomer), (±)-**24**, *dl*-**40**, and **57** were carried out by single-crystal X-ray diffraction at 298(2) K (for (±)-**24**, *dl*-**40** and **57**) or at 150(2) K (for the remaining compounds) using a Bruker X8-Apex four-circle diffractometer equipped with Mo Kα generator (λ=0.71073 Å), area detector, and Kryo-Flex cryostat. Structure solution and refinement (on F_0^2) were based on standard methods.[42–44] All nonhydrogen atoms were treated anisotropically, with the exception of the disordered carbons in the lowest-occupancy sites of **57**. Hydrogen atoms were treated isotropically and either located in ΔF maps or set to idealised positions (with torsion angle refinement for methyl groups in (±)-**24**). In the latter case, their displacement parameters were constrained to be 50% and 20% larger than those of the parent carbon atom for CH_3 and CH_2/CH groups, respectively. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications nos. CCDC 868795–868802. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Products **14a**,[29b,45] **14b**,[46] **15a**,[47] **15b**,[47] H-**17a**,[29b,48] H-**17b**,[49] **18a**,[50] **18b**,[51] **19a**,[52] **19b**,[53] **52**,[54] **66**,[55] **67**,[54] **68**,[56] **69**,[57] and phenylthioacetamide[58] are known compounds.

4.2. Preparation of cyclic imidates, amidines, and thioimidates

*4.2.1. Preparation of 2-ethyl-4,5-dihydrooxazole (**14a**).*[24] Ethyl orthopropionate (50.0 mmol, 9.9 mL), 2-aminoethanol (50.0 mmol, 3.0 mL), and acetic acid (3.0 mmol, 173 μL) were injected, under Argon, in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirring bar. The apparatus was then heated with an oil bath, thermostated at 105 °C. After 24 h, the reaction mixture was cooled. Distillation, under atmospheric pressure, gave the product **14a**,[29b,45] as a colorless liquid (3.71 g, 75%), bp 123–126 °C.

*4.2.2. Preparation of 2-ethyl-5,6-dihydro-4H-1,3-oxazine (**14b**).*[24] Ethyl orthopropionate (120.0 mmol, 23.9 mL), 2-aminopropanol (100.0 mmol, 7.6 mL), and acetic acid (6 mmol, 346 μL) were injected, under Argon, in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirring bar. The apparatus was then heated with an oil bath, thermostated at 105 °C. After 24 h, the reaction mixture was cooled at 0 °C and, under stirring, HCl_{aq} 10% (30 mL) was added. Then it was washed with DCM (3×50 mL), neutralized with $NaOH_{aq}$ 10% (30 mL), and extracted in continuous with DCM, overnight. The organic phase was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The remaining yellow oil was the product **14b**[46] (7.75 g, 69%), pure enough to be used for subsequent acylation.

*4.2.3. Preparation of 2-benzyl-4,5-dihydrooxazole (**15a**).*[25a] In a three-necked round bottom flask, fitted with an Argon inlet tap, a condenser, with a $CaCl_2$ tube on the top, and a dropping funnel, was weighed anhydrous $ZnCl_2$ (5.0 mmol, 0.68 g) and chlorobenzene (40 mL) was introduced. To the stirred mixture were added, under argon, phenylacetonitrile (120.0 mmol, 13.9 mL) and, slowly, a solution of 2-aminoethanol (100.0 mmol, 6.0 mL) in chlorobenzene (10 mL). The flask was heated at reflux with an oil bath, thermostated at 130 °C. After 18 h, the mixture was cooled and the chlorobenzene distilled off under reduced pressure. The crude residue was chromatographed on silica gel, eluting with a petroleum ether (PE: bp 40–60 °C)/diethyl ether (Et_2O) gradient (from 50:50 to 0:100). Product **15a**[47] was recovered as a yellow liquid (5.77 g, 36%). It was pure enough to be used for subsequent acylation.

*4.2.4. Preparation of 2-benzyl-5,6-dihydro-4H-1,3-oxazine (**15b**).*[25a] Following the same procedure used for the preparation of **15a**, anhydrous $ZnCl_2$ (5.0 mmol, 0.68 g), phenylacetonitrile (100.0 mmol, 11.7 mL), and a solution of 3-aminopropanol (100.0 mmol, 7.6 mL) in chlorobenzene (50 mL) were processed at 130 °C (20 h). The cooled reaction mixture was acidified with HCl_{aq} 10% (35 mL), washed with DCM (2×50 mL), treated with $NaOH_{aq}$ 10% (30 mL), and extracted with DCM (4×50 mL). The aqueous phase was further continuously extracted with DCM, overnight. The organic phases were collected, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Product **15b**[47] was recovered as a yellow liquid (8.93 g, 51%). It was pure enough to be used for the next acylation.

*4.2.5. Preparation of 2-ethylimidazoline acetate (**18a**).*[26] In a three-necked round bottom flask, fitted with an argon inlet tap, a condenser, mounting a $CaCl_2$ tube, and a dropping funnel, were introduced under Argon, and stirring, CH_3CN (50 mL), ethyl orthopropionate (53.0 mmol, 10.5 mL), acetic acid (53.0 mmol, 3.1 mL) and, slowly, 1,2-diaminoethane (50.0 mmol, 3.4 mL). A white precipitate, which hindered the agitation, developed. The reaction mixture was then heated at reflux with an oil bath, thermostated at 85 °C (the white precipitate, on heating, solubilized). After 2 h, it was cooled and the solvent distilled off at reduced pressure. The crude oil was diluted with DCM and refluxed for some minutes. The white precipitate of 1,2-ethylendiammonium diacetate, in suspension, was filtered off. The filtrate was concentrated at reduced pressure, giving the product **18a**,[50] as a yellow oil (6.92 g, 88%). It was pure enough to be used for the next acylation.

*4.2.6. Preparation of 2-ethyl-1,4,5,6-tetrahydropyrimidine acetate (**18b**).*[26] Following the same procedure used for the preparation of **18a**, CH_3CN (50 mL), ethyl orthopropionate (41.0 mmol, 8.2 mL), acetic acid (41.0 mmol, 2.4 mL), and 1,3-diaminopropane (39.0 mmol, 3.3 mL) were processed at 85 °C per 2 h. The solvent was then distilled off from the reaction mixture, at reduced pressure. The unreacted diamine was separated as the diacetate, after crystallization in DCM (with few mL of CH_3OH). Product **18b**[51] was recovered, after evaporation of the filtrate, under reduced pressure, as a white solid (6.04 g, 90%). It was pure enough to be used for the next acylation.

4.2.7. Preparation of phenylthioacetamide.[28] *Warning: the original procedure gave rise to an explosive reaction, using a closed Schlenk; moreover it always afforded the ester! It was thus modified as here reported.* In a round bottom flask, fitted with a condenser, phenylacetonitrile (60.0 mmol, 6.9 mL), diethyldithiophosphoric acid 90%

(60 mmol, 10.3 mL), and H_2O (60.0 mmol, 1.1 mL) were added in sequence, under stirring. The reaction mixture was heated with an oil bath, thermostated at 85–90 °C (5 h); during this time it passed from cloudy gray to clear yellow-orange. The flask was then cooled and the crude mixture directly chromatographed on silica gel, eluting with a PE/DCM gradient (from 50:50 to 0:100). The phenylthioacetamide[58] was recovered as a pale yellow fluffy solid, which was still further purified by crystallization from DCM/*n*-hexane, giving a white crystalline solid (5.50 g, 61%).

*4.2.8. Preparation of 2-benzylimidazoline (H-**17a**).*[29] In a round bottom flask, fitted with a condenser, phenylthioacetamide (17.0 mmol, 2.57 g), anhydrous THF (17 mL), and 1,2-diaminoethane (20.4 mmol, 1.4 mL) were added in sequence, under stirring. The reaction mixture was heated with an oil bath, thermostated at 80 °C (16 h); during this time its colour passed from clear yellow to bright green-yellow. Besides, along the condenser, a patina of $(NH_4)_2S$ deposited (this salt comes from the reaction between the gases NH_3 and H_2S, evolved during the transformation). The flask was then cooled. Afterward the solvent was evaporated, under reduced pressure. The crude reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (3×50 mL). The organic phases were collected, dried over $MgSO_4$, and filtered. The solvent was finally distilled off, under reduced pressure, giving the product H-**17a**,[29b,48] as a yellow-orange solid (2.69 g, 99%). It was pure enough to be used for the next acylation.

*4.2.9. Preparation of 2-benzy1,4,5,6-tetrahydropirymidine (H-**17b**).*[29] Following the same procedure used for the preparation of H-**17a**, phenylthioacetamide (20.0 mmol, 3.02 g), anhydrous THF (20 mL), and 1,3-diaminopropane (24.0 mmol, 2.0 mL) were processed at 80 °C (16 h). The product H-**17b**[49] was recovered as a yellowish solid (2.17 g, 62%). It was pure enough to be used for the next acylation.

*4.2.10. Preparation of 2-benzyl-4,5-dihydrothiazole (**19a**).*[30] In a Schlenk tube were poured EtOH (50 mL) and then, under argon, was slowly added Na^0 (120.0 mmol, 2.76 g). Afterward the solution of EtONa was transferred into a round bottom flask fitted with a condenser. The flask was placed in an ice-bath. Cysteamine hydrochloride (100.0 mmol, 11.36 g), phenylacetonitrile (300.0 mmol, 34.6 mL), and ammonium acetate (60.0 mmol, 4.62 g) were slowly introduced in sequence, and under stirring. The solution was heated at reflux with an oil bath, thermostated at 85 °C (16 h). Then, the reaction mixture was cooled, concentrated under reduced pressure, and diluted with Et_2O (100 mL). The suspension was washed with brine (2×50 mL) and the aqueous phases, collected, were extracted with Et_2O (50 mL). The organic phases were put together, dried over Na_2SO_4, filtered, and concentrated. The product **19a**[52] was separated from the phenylacetonitrile excess through distillation under reduced pressure (bp 140 °C, 5 mmHg), and recovered as a colorless liquid—on aging it took a bright yellow coloration—(12.88 g, 73%); δ_H (200 MHz, $CDCl_3$) 3.25 (2H, t, *J* 8.4 Hz, CH_2), 3.83 (2H, br s, CH_2Ph), 4.24 (2H, tt, *J* 8.4, 1.3 Hz, CH_2), 7.20–7.40 (5H, m, 5CHAr); *m*/*z* (EI, 70 eV) 177 [100, M^+], 149 (67), 117 (38), 91 (54), 60 (82%).

*4.2.11. Preparation of 2-benzyl-5,6-dihydro-4H-1,3-thiazine (**19b**).*[30] In a Schlenk tube, where 3 Å sieve (3.6 g) were previously weighed in, 3-aminopropanol (80.0 mmol, 6.1 mL) and methyl phenylacetate (46.0 mmol, 6.6 mL) were added under argon. The stirred solution was then heated with an oil bath, thermostated at 160 °C (16 h). Afterward the reaction mixture was cooled, diluted with hot MeOH, and filtered on Celite. The solution, evaporated under reduced pressure, gave a waxy white solid (10.72 g), containing the *N*-(3-hydroxypropyl)-phenylacetamide. All the crude hydroxyamide was loaded into a round bottom flask, fitted with an argon inlet tap and a condenser, with a KOH tube on the top (to stop the H_2S released during the thionation). Afterward, toluene (200 mL) and the Lawesson's reagent (46.0 mmol, 18.61 g) were added in sequence, under argon and vigorous stirring. The suspension was heated at reflux with an oil bath, thermostated at 120 °C. After 1.5 h the reaction mixture was cooled and K_2CO_{3aq} 2 M (150 mL) added. It was then stirred for further 30 min, at room temperature. The organic phase was separated, and the aqueous phase extracted with Et_2O (3×100 mL). The organic phases were combined and extracted with HCl_{aq} 10% (3×100 mL). The acid aqueous phases were combined, basified with $NaOH_{aq}$ 5% (400 mL), and extracted with Et_2O (3×150 mL). The organic phases were collected, dried over $MgSO_4$, and evaporated, under reduced pressure. The product **19b**[53] was recovered as a bright yellow oil (4.41 g, overall yield 50%)—it was pure enough to be used for the next acylation—; δ_H (200 MHz, $CDCl_3$) 1.69 (2H, qn, *J* 5.8 Hz, $CH_2CH_2CH_2$), 2.88 (2H, t, *J* 5.8 Hz, CH_2), 3.60 (2H, s, CH_2Ph), 3.64 (2H, t, *J* 5.8 Hz, CH_2), 7.10–7.35 (5H, m, 5CHAr); *m*/*z* (EI, 70 eV) 190 [70, $(M-H)^+$], 174 (12), 163 (49), 144 (18), 117 (22), 91 (100), 74 (29%).

4.3. Preparation of *N*-α-perchloroacyl ketene-*N*,X-acetals

*4.3.1. Preparation of 3-(2,2-dichlorobutanoyl)-2-ethylidenoxazolidine (**9a**).* 2-Ethyl-4,5-dihydrooxazole (**14a**) (30 mmol, 2.97 g) was weighed in a Schlenk tube. Anhydrous DCM (30 mL) and triethylamine (TEA) (36 mmol, 5 mL) were then added under argon. The mixture was cooled at 0 °C in a ice-bath and a solution of 2,2-dichlorobutanoyl chloride (30 mmol, 5.26 g) in anhydrous DCM (5 mL) was slowly added with a syringe pump (30 min). The reaction mixture was then stirred at room temperature for 17 h. Afterward $NaOH_{aq}$ 5% (30 mL) was added and the product extracted with DCM (3×50 mL). The organic phases were collected, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Crude product **9a** was recovered as an orange oil (6.38 g, 89%), and used immediately as such in the next RC (it cannot be purified by chromatography); *m*/*z* (EI, 70 eV) 237 (40, M^+), 202 (100), 126 (16), 111 (22), 103 (81), 98 (72), 75 (34), 70 (25%).

*4.3.2. Preparation of 3-(2,2-dichlorobutanoyl)-2-ethyliden-1,3-oxazinane (**9b**).* Following the same procedure used for the preparation of **9a**, 2-ethyl-5,6-dihydro-4*H*-[1,3]oxazine (**14b**) (30 mmol, 3.39 g), TEA (36 mmol, 5 mL), and 2,2-dichlorobutanoyl chloride (30 mmol, 5.26 g), in anhydrous DCM (30+5 mL), gave crude **9b** (it cannot be purified by chromatography and was used immediately as such in the next RC), as a dark orange oil, mixture of rotamers (6.52 g, 86%); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, br t, *J* 7.0 Hz, CH_2CH_3), 1.63 (3H, br d, *J* 6.9 Hz, CH_3CH=), 1.85–2.05 (2H, br m, CH_2), 2.49 (2H, br q, *J* 7.0 Hz, CH_2CH_3), 3.87 (2H, br s, CH_2), 4.00–4.10 (2H, br m, CH_2), 5.07 (1H, br s, CH=); δ_C (100.62 MHz, $CDCl_3$) 9.6, 9.8, 25.1, 40.2, 46.4, 67.8, 85.5, 104.7, 144.2, 164.3; *m*/*z* (EI, 70 eV) 216 [7, $(M-Cl)^+$], 180 (2), 140 (100), 112 (52), 84 (54%).

*4.3.3. Preparation of 3-(2,2-dichlorobutanoyl)-2-benzylidenoxazolidine (**12a**).* Following the same procedure used for the preparation of **9a**, 2-benzyl-4,5-dihydrooxazole (**7a**) (23.0 mmol, 3.71 g), TEA (27.6 mmol, 3.8 mL), and 2,2-dichlorobutanoyl chloride (23.0 mmol, 4.04 g), were processed in anhydrous DCM (30+5 mL). The recovered crude was purified by flash chromatography on silica gel, eluting with PE/Et_2O 70:30. Product **12a** (3.46 g, 50%) was isolated, as a yellowish solid with a small amount of unseparable hydrolyzed adduct (0.70 g, 10%) (**12a**/hydrolysis adduct=84:16). A clean sample of **12a** was obtained by crystallization, under argon, from DCM/hexane at 4 °C [HRMS found 300.0555. $C_{14}H_{16}Cl_2NO_2$ $(M+H)^+$ requires 300.0553]; R_f (50% PE/Et_2O) 0.55; mp 103.3–105.7 °C; ν_{max} (KBr) 1679 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31

(3H, t, *J* 7.0 Hz, CH_2CH_3), 2.58 (2H, q, *J* 7.0 Hz, CH_2CH_3), 4.38 (2H, t, *J* 6.8 Hz, CH_2), 4.53 (2H, t, *J* 6.8 Hz, CH_2), 6.56 (1H, s, PhCH=), 7.11 (1H, t, *J* 7.4 Hz, CH_{Ar}), 7.20–7.40 (2H, m, $2CH_{Ar}$), 7.55 (2H, d, *J* 7.2 Hz, $2CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) 9.5, 38.3, 47.4, 66.2, 86.7, 91.7, 125.1, 128.2, 128.7, 135.9, 147.7, 161.1; *m*/*z* (EI, 70 eV) 299 (43, M^+), 264 (34), 162 (59), 132 (100), 117 (29), 103 (51), 91 (62), 77 (24%). Selected crystallographic data: $C_{14}H_{15}Cl_2NO_2$, *M*=300.17, monoclinic, space group $P2_1/c$, *a*=11.0253(4), *b*=10.9833(5), *c*=11.7154(4) Å, *β*=105.7931(12)°, *V*=1365.11(9) Å^3, *Z*=4, *T*=150(2) K, ρ_{calcd}=1.461 g cm^{-3}; reflections collected/unique 14,001/3137 (R_{int}=0.0220); final *R* indices R_1=0.0249 [$I>2\sigma(I)$], wR_2=0.0713 (all data); data/restraints/parameters=3137/0/232, GoF=1.055, residuals min/max=−0.222/0.284 e Å^{-3}.

*4.3.4. Preparation of 3-(2,2-dichlorobutanoyl)-1-(tert-butyloxycarbonyl)-2-ethylidenimidazolidine (Boc-**10a**).* A Schlenk tube was connected to an argon line through a $CaCl_2$ trap. Under an inert atmosphere, it was added to a solution of 2-ethylimidazoline acetate (**18a**) (29.3 mmol, 4.63 g) in anhydrous DCM (25 mL) and TEA (33.7 mmol, 4.7 mL). The tube was cooled with an ice-bath and a solution of di-*tert*-butyl dicarbonate [$(Boc)_2O$] (33.7 mmol, 7.35 g) in anhydrous DCM (5 mL) was injected under stirring. When the strong effervescence (due to the released CO_2) subsided, the Schlenk tube (together the $CaCl_2$ trap) was parted from the Argon line. The mixture was stirred at room temperature for 14 h, afterward it was diluted with H_2O (30 mL) and extracted with DCM (3×30 mL). The organic phases were collected and washed with $NaHCO_{3aq}$ satd (30 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Then, following the same procedure used for the preparation of **9a**, the crude 1-(*tert*-butyloxycarbonyl)-2-ethylimidazoline (Boc-**16a**), recovered (6.78 g), as a yellow oil, was solubilized in anhydrous DCM (15 mL) and reacted with TEA (35.2 mmol, 4.9 mL) and a solution of 2,2-dichlorobutanoyl chloride (29 mmol, 5.14 g) in anhydrous DCM (5 mL). The reaction mixture, after stirring for 18 h at room temperature, was diluted with H_2O (25 mL) and extracted with DCM (3×25 mL). The organic phases were collected, dried over $MgSO_4$, filtered, and concentrated. The crude was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 99:1 to 50:50). The product Boc-**10a** was recovered as a white-yellowish solid (4.05 g, overall yield 41%), mixture of two diastereomers (dr 74:26) [HRMS found 337.1078. $C_{14}H_{23}Cl_2N_2O_3$ $(M+H)^+$ requires 337.1080]; R_f (50% PE/Et_2O) 0.60, and of the hydrolysis adduct Boc-**20a** (Boc-**10a**/Boc-**20a**=88:12). Boc-**20a** was also present in other fractions: its overall yield was 34% (3.54 g). When chromatographed Boc-**16a** was used, the yield of Boc-**10a** increased to 66%, without Boc-**20a**, and with a dr=91:9.

*4.3.4.1. 3-(2,2-Dichlorobutanoyl)-1-(tert-butyloxycarbonyl)-2-ethylidenimidazolidine (Boc-**10a**).* ν_{max} (KBr) 1719, 1692, 1671 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *major diastereomer* 1.18 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.46 (3H, d, *J* 7.2 Hz, CH_3CH=), 1.49 (9H, s, $C(CH_3)_3$), 2.55 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.63 (2H, t, *J* 6.8 Hz, NCH_2), 4.23 (2H, t, *J* 6.8 Hz, NCH_2), 5.89 (1H, br s, CH_3CH=), *minor diastereomer* 1.23 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.54 (9H, s, $C(CH_3)_3$), 1.67 (3H, d, *J* 7.3 Hz, CH_3CH=), 2.44 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.77 (2H, t, *J* 6.6, NCH_2), 4.15–4.25 (2H, m, NCH_2), 6.31 (1H, q, *J* 7.3 Hz, CH_3CH=); δ_C (100.62 MHz, $CDCl_3$) *major diastereomer* 9.7, 13.9, 28.3, 40.5, 45.3, 46.8, 81.7, 86.2, 98.7, 133.1, 151.4, 161.2, *minor diastereomer* 9.6, 14.4, 28.2, 39.7, 44.9, 46.8, 83.9, 87.0, 103.1, 134.3, 152.5, 161.6; *m*/*z* (EI, 70 eV) 336 (2, M^+), 301 (4), 245 (46), 201 (18), 57 (100%).

*4.3.5. Preparation of 3-(2,2-dichlorobutanoyl)-1-acetyl-2-ethylidenimidazolidine (Ac-**10a**).* Following the procedure used for preparing Boc-**10a**, 1-acetyl-2-ethylimidazoline Ac-**16a** was prepared by treating a solution of 2-ethylimidazoline acetate (**18a**) (33.8 mmol, 5.35 g) and TEA (72.7 mmol, 10.1 mL), in anhydrous DCM (30 mL), with a solution of acetic anhydride (38.9 mmol, 3.7 mL) in anhydrous DCM (2 mL) added with a syringe pump (45 min). The reaction was worked-up after 19 h. Afterward, following the same protocol utilized for Boc-**16a**, the crude 1-acetyl-2-ethylimidazoline (Ac-**16a**),[59] recovered (4.95 g) as a yellow-orange oil, was reacted with TEA (41 mmol, 5.7 mL) and 2,2-dichlorobutanoyl chloride (34 mmol, 5.96 g), in anhydrous DCM (30+5 mL). After 17 h at room temperature, the reaction mixture was diluted with H_2O (30 mL) and $NaOH_{aq}$ 5% (10 mL), and extracted with DCM (3×30 mL). The crude mixture, obtained from the collected organic phases, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 90:10 to 40:60). The product Ac-**10a** was recovered as an orange oil (4.88 g, overall yield 52%) (mixture of rotamers of diastereomers) [HRMS found 279.0655. $C_{11}H_{17}Cl_2N_2O_2$ $(M+H)^+$ requires 279.0662]; R_f (10% PE/Et_2O) 0.33, together with the hydrolysis adduct Ac-**20a** (1.47 g, 15%) R_f (10% PE/Et_2O) 0.16 (Ac-**10a**/Ac-**20a**=78:22).

*4.3.5.1. 3-(2,2-Dichlorobutanoyl)-1-acetyl-2-ethylidenimidazolidine (Ac-**10a**).* ν_{max} (film) 1699, 1668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14–1.26 (3H, m, CH_2CH_3), 1.40–1.75 (3H, br m, CH_3CH=), 2.00–2.35 (3H, br m, CH_3C=O), 2.45–2.60 (2H, m, CH_2CH_3), 3.72 (2H, t, *J* 6.6 Hz, NCH_2), 4.30 (2H, br s, NCH_2), 5.16 (1H, br s, *isomer a* CH=), 6.33 (1H, q, *J* 7.2 Hz, *isomer b* CH=), 6.43 (1H, br s, *isomer c* CH=), 6.56 (1H, q, *J* 7.4 Hz, *isomer d* CH=); δ_C (100.62 MHz, $CDCl_3$) 9.3, 9.5, 13.8, 14.2, 14.5, 22.7, 24.1, 39.0, 39.4, 43.1, 45.6, 46.3, 46.6, 85.9, 86.5, 102.3 (*isomer c* CH=), 104.0 (*isomer b* CH=), 104.6 (*isomer d* CH=), 105.1 (*isomer a* CH=), 133.2, 134.2, 160.9, 167.3, 168.1; *m*/*z* (EI, 70 eV) 278 (5, M^+), 243 (81), 201 (100), 165 (29%).

*4.3.6. Preparation of (Z)-3-(2,2-dichlorobutanoyl)-1-acetyl-2-benzylidenimidazolidine (**13a**).* Following the procedure used for preparing Ac-**10a**, 2-phenylmethylimidazoline (H-**17a**) (15.85 mmol, 2.54 g) was treated with TEA (19.2 mmol, 2.7 mL) and acetic anhydride (18.2 mmol, 1.72 mL), in anhydrous DCM (16+3 mL—the second value is referred to the solvent used to dilute the acylating reagent). Afterward, as described for the preparation of Boc-**10a**, the crude 1-acetyl-2-benzylimidazoline (Ac-**17a**), recovered as a honey-yellow oil (3.33 g), was reacted with TEA (19.0 mmol, 2.7 mL) and 2,2-dichlorobutanoyl chloride (15.8 mmol, 2.77 g), in anhydrous DCM (15+4 mL). The crude mixture, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with DCM/Et_2O 90:10. The enamide **13a** (2.85 g, overall yield 53%) was isolated as a white fluffy solid (mixture of rotamers) [HRMS found 363.0645. $C_{16}H_{18}Cl_2N_2NaO_2$ $(M+Na)^+$ requires 363.0638]; R_f (50% DCM/Et_2O) 0.53; mp 178–179 °C; ν_{max} (KBr) 1689, 1664 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.24 (3H, br s, CH_3C=O), 2.32 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.82 (2H, t, *J* 6.3 Hz, CH_2), 4.46 (2H, t, *J* 6.3 Hz, CH_2), 7.11 (1H, br s, CH_{Ar}), 7.15–7.30 (4H, m, $4CH_{Ar}$), 7.63 (1H, br s, CH=); δ_C (100.62 MHz, $CDCl_3$) 9.5, 24.7, 39.4, 44.3, 86.1, 106.8, 126.3, 127.4, 128.2, 133.1, 136.8, 160.5, 167.8.

*4.3.7. Preparation of 1-(tert-butyloxycarbonyl)-3-(2,2-dichlorobutanoyl)-2-ethyliden-1,3-diazinane (Boc-**10b**).* Following the procedure used to prepare Ac-**10a**, 2-ethyl-1,4,5,6-tetrahydropyrimidine acetate (**18b**) (28.4 mmol, 4.89 g), was treated with TEA (32.7 mmol, 4.55 mL) and di-*tert*-butyl dicarbonate $(Boc)_2O$ (32.7 mmol, 7.13 g), in anhydrous DCM (20+5 mL). The 1-*tert*-butoxycarbonyl-2-ethyl-1,4,5,6-tetrahydropyrimidine (Boc-**16b**), thus prepared and isolated, after flash chromatography (eluting with a PE/Et_2O gradient, from 90:10 to 40:60) as a yellow oil (3.62 g, 60%), was reacted with TEA (20.1 mmol, 2.8 mL) and 2,2-dichlorobutanoyl chloride (17.0 mmol, 2.98 g) in anhydrous DCM (15+5 mL). The raw Boc-**10b**, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 99:1 to 50:50). The enamide Boc-**10b** was recovered as a yellow oil (3.15 g, overall yield

32%), mixture of rotamers of diastereomers (dr 60:40) [HRMS found 373.1061. $C_{15}H_{24}Cl_2N_2NaO_3$ $(M+Na)^+$ requires 373.1056]; R_f (50% PE/Et_2O) 0.5; ν_{max} (film) 1696, 1668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *major diastereomer* 1.12–1.25 (3H, m, CH_2CH_3), 1,41 (9H, s, $C(CH_3)_3$), 1.45–1.55 (3H, br m, CH_3CH=), 1.75–1.95 (2H, br m, CH_2), 2.47 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.30–4.30 (4H, br m, $2NCH_2$), 5.59 (1H, br q, *J* 6.4 Hz, CH=), *minor diastereomer* 1.12–1.25 (3H, m, CH_2CH_3), 1.42 (9H, s, $C(CH_3)_3$), 1.64 (3H, d, *J* 6.8 Hz, CH_3CH=), 1.75–1.95 (2H, br m, CH_2), 2.47 (2H, q, *J* 7.1 Hz, CH_2CH_3), 3.30–4.30 (4H, br m, $2NCH_2$), 5.67 (1H, br q, *J* 6.8 Hz, CH=); δ_C (100.62 MHz, $CDCl_3$) *major diastereomer* 9.50, 12.4, 24.3, 28.2, 39.6, 44.6, 48.6, 80.4, 85.8, 119.8, 132.4, 153.8, 163.4, *minor diastereomer* 9.55, 13.1, 23.6, 28.2, 39.7, 44.6, 49.0, 80.5, 85.9, 122.0, 131.7, 153.8, 163.4.

*4.3.8. Preparation of 1-acetyl-3-(2,2-dichlorobutanoyl)-2-ethylidene-1,3-diazinane (Ac-**10b**).* Following the procedure used to prepare Ac-**10a**, 2-ethyl-1,4,5,6-tetrahydropyrimidine acetate (**18b**) (21.7 mmol, 3.74 g) was treated with TEA (47.0 mmol, 6.55 mL) and acetic anhydride (25.4 mmol, 2.4 mL), in anhydrous DCM (20+2 mL). The crude 1-acetyl-2-ethyl-1,4,5,6-tetrahydropyrimidine (Ac-**16b**),[59] thus prepared and isolated as a light yellow oil (2.26 g), was reacted with TEA (17.6 mmol, 2.45 mL) and 2,2-dichlorobutanoyl chloride (14.7 mmol, 2.58 g) in anhydrous DCM (15+3 mL). The raw Ac-**10b**, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 99:1 to 10:90). The enamide Ac-**10b** (3.43 g, overall yield 54%) was secured as a light brown wax, mixture of rotamers of diastereomers (*Z*/*E* 64:36) [HRMS found 293.0819. $C_{12}H_{19}Cl_2N_2O_2$ $(M+H)^+$ requires 293.0818]; R_f (50% PE/Et_2O) 0.14; ν_{max} (film) 1693, 1662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *Z isomer* 1.21 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.55 (3H, d, *J* 7.0 Hz, CH_3CH=), 1.84 (2H, br s, CH_2), 2.20 (3H, s, CH_3C=O), 2.45 (2H, q, *J* 7.2 Hz, CH_2CH_3), 2.70–5.20 (4H, br s, $2NCH_2$), 5.55 (1H, q, *J* 7.0 Hz, CH=), *E isomer* 1.20 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.70 (3H, d, *J* 7.1 Hz, CH_3CH=), 1.90–2.10 (2H, m, CH_2), 2.14 (3H, s, CH_3C=O), 2.43 (2H, q, *J* 7.1 Hz, CH_2CH_3), 2.90 (1H, dt, *J* 12.2 Hz, 3.3, NC*H*H), 3.53 (1H, m, NC*H*H), 4.61 (1H, br d, *J* 12.2 Hz, NCH*H*), 4.85 (1H, br dt, *J* 13.2, 3.6 Hz, NCH*H*), 5.65 (1H, q, *J* 7.1 Hz, CH=); δ_C (100.62 MHz, $CDCl_3$) *Z isomer* 9.5, 12.2, 21.8, 24.5, 39.3, 43.2, 49.5, 85.3, 122.0, 134.8, 162.4, 169.9; *E isomer* δ=9.4, 12.8, 21.3, 24.5, 39.28, 43.1, 50.1, 85.5, 122.9, 134.4, 163.7, 170.0; *m*/*z* (EI, 70 eV) 277 [5 $(M-Me)^+$], 257 (16), 220 (30), 177 (75), 153 (62), 139 (100), 111 (69), 43 (36%). Following crystallization, under argon, from DCM/hexane at 4 °C, gave a clean sample of the major diastereomer (*Z*) of Ac-**10b** (yellow-orange solid, mp 75–80 °C), suitable for single-crystal X-ray diffraction, was obtained. Selected crystallographic data: $C_{12}H_{18}Cl_2N_2O_2$, *M*=293.18, monoclinic, space group $P2_1/c$, *a*=12.2802(3), *b*=8.8798(2), *c*=13.1289(3) Å, β=92.1881(8)°, *V*=1430.61(6) $Å^3$, *Z*=4, *T*=150(2) K, ρ_{calcd}=1.361 g cm^{-3}; reflections collected/unique 20,181/4549 (R_{int}=0.0240); final *R* indices R_1=0.0286 [$I>2\sigma(I)$], wR_2=0.0830 (all data); data/restraints/parameters=4549/0/235, GoF=1.047, residuals min/max=−0.253/0.316 e $Å^{-3}$.

*4.3.9. Preparation of 1-acetyl-3-(2,2-dichlorobutanoyl)-2-benzylidene-1,3-diazinane (**13b**).* Following the procedure used to prepare Ac-**10a**, 2-benzyl-1,4,5,6-tetrahydropyrimidine (H-**17b**) (12.45 mmol, 2.17 g), was treated with TEA (15.0 mmol, 2.1 mL) and acetic anhydride (14.3 mmol, 1.35 mL), in anhydrous DCM (10+3 mL). The crude 1-acetyl-2-benzyl-1,4,5,6-tetrahydropyrimidine (Ac-**17b**), thus prepared and isolated as orange oil (2.52 g), was made react with TEA (14.0 mmol, 2.0 mL) and 2,2-dichlorobutanoyl chloride (11.7 mmol, 2.05 g), in anhydrous DCM (13+2 mL). The raw material, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 99:1 to 50:50). The enamide **13b** was isolated as the *E* isomer (0.53 g, overall yield 12%), orange oil (mixture of rotamers) [HRMS found 355.0973. $C_{17}H_{21}Cl_2N_2O_2$ $(M+H)^+$ requires 355.0975], R_f (50% PE/Et_2O) 0.22, as the *Z* isomer (1.18 g, overall yield 27%), white cream solid (mixture of rotamers) [HRMS found 355.0970]. $C_{17}H_{21}Cl_2N_2O_2$ $(M+H)^+$ requires 355.0975], R_f (50% PE/Et_2O) 0.11 and as a mixture of the two geometric diastereomers (*Z*/*E* 43:57) (0.85 g, overall yield 19%). A clean sample of *Z*-**13b** was obtained by crystallization, under argon, from DCM/hexane at 4 °C, mp 140–141 °C.

*4.3.9.1. (Z)-1-Acetyl-3-(2,2-dichlorobutanoyl)-2-benzyliden-1,3-diazinane (Z-**13b**).* ν_{max} (KBr) 1653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.70–2.30 (2H, br m, CH_2), 2.38 (2H, q, *J* 7.2 Hz, CH_2CH_3), 2.40 (3H, s, CH_3C=O), 3.20 (1H, br s, NCC*H*H), 3.73 (1H, br s, NC*H*H), 4.64 (1H, br s, NCH*H*), 4.95 (1H, br s, NCH*H*), 6.41 (1H, s, CH=), 7.20–7.40 (5H, m, $5CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) 9.5, 22.1, 24.5, 39.4, 43.5, 49.7, 85.4, 125.7, 127.9, 128.6, 132.8, 134.1, 162.5, 169.7. Selected crystallographic data: $C_{17}H_{20}Cl_2N_2O_2$, *M*=355.25, monoclinic, space group $P2_1/c$, *a*=12.4406(3), *b*=7.23420(10), *c*=19.4493(4) Å, β=90.1283(8)°, *V*=1750.39(6) $Å^3$, *Z*=4, *T*=150(2) K, ρ_{calcd}=1.348 g cm^{-3}; reflections collected/unique 30,531/5598 (R_{int}=0.0232); final *R* indices R_1=0.0303 [$I>2\sigma(I)$], wR_2=0.0873 (all data); data/restraints/parameters=5598/0/288, GoF=1.053, residuals min/max=−0.322/0.347 e $Å^{-3}$.

*4.3.9.2. (E)-1-Acetyl-3-(2,2-dichlorobutanoyl)-2-benzyliden-1,3-diazinane (E-**13b**).* ν_{max} (film) 1644 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.70–2.00 (1H, m, C*H*H), 1.94 (3H, s, CH_3C=O), 2.05–2.25 (1H, m, CH*H*), 2.56 (2H, q, *J* 7.1, CH_2CH_3), 3.10–3.35 (1H, br m, NC*H*H), 3.65–3.90 (1H, br m, NC*H*H), 4.74 (1H, br dt, *J* 12.6, 4.4 Hz, NCH*H*), 4.91 (1H, br dt, *J* 13.4, 4.2 Hz, NCH*H*), 6.54 (1H, s, CH=), 7.20–7.50 (5H, m, $5CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) 9.3, 21.3, 24.2, 39.2, 42.9, 50.0, 85.5, 126.1, 127.9, 128.6, 128.9, 132.9, 133.1, 163.5, 169.7.

*4.3.10. Preparation of 3-(2,2-dichlorobutanoyl)-2-(Z)-benzylidenthiazolidine (**11a**).* Following the procedure used to acylate Boc-**16a**, 2-benzyl-4,5-dihydrothiazole (**19a**) (30.0 mmol, 5.31 g) was treated with TEA (36.0 mmol, 5.0 mL) and 2,2-dichlorobutanoyl chloride (30.0 mmol, 5.26 g) in anhydrous DCM (30+2 mL). The raw material, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 95:5 to 90:10). The enamide **11a** was isolated as a white solid (8.81 g, 93%) [HRMS found 316.0314. $C_{14}H_{16}Cl_2NOS$ $(M+H)^+$ requires 316.0324]; R_f (20% PE/Et_2O) 0.77; mp 78–80 °C; ν_{max} (KBr) 1659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.59 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.16 (2H, t, *J* 6.2 Hz, CH_2), 4.53 (2H, t, *J* 6.2 Hz, CH_2), 7.15–7.25 (1H, m, CH_{Ar}), 7.30–7.40 (3H, m, $2CH_{Ar}$+CH=), 7.40–7.50 (2H, m, $2CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) 9.6, 29.2, 39.5, 51.8, 87.3, 116.2, 126.4, 128.1, 128.3, 135.6, 136.5, 162.7; *m*/*z* (EI, 70 eV) 315 (24, M^+), 280 (30), 244 (6), 176 (100), 148 (40%). A clean sample of **11a**, for single-crystal X-ray diffraction, was obtained by crystallization, under argon, from DCM/hexane at 4 °C. The crystallographic analysis at 150(2) K revealed the occurrence of two packing polymorphs, which crystallize in the same space group. Selected crystallographic data for polymorph **I**: $C_{14}H_{15}Cl_2NOS$, *M*=316.23, monoclinic, space group $P2_1/c$, *a*=6.2101(2), *b*=25.1112(7), *c*=9.4928(3) Å, β=94.8705(11)°, *V*=1474.99(8) $Å^3$, *Z*=4, *T*=150(2) K, ρ_{calcd}=1.424 g cm^{-3}; reflections collected/unique 15,623/3592 (R_{int}=0.0205); final *R* indices R_1=0.0308 [$I>2\sigma(I)$], wR_2=0.0788 (all data); data/restraints/parameters=3592/0/232, GoF=1.072, residuals min/max=−0.255/0.284 e $Å^{-3}$. Selected crystallographic data for polymorph **II**: $C_{14}H_{15}Cl_2NOS$, *M*=316.23, monoclinic, space group $P2_1/c$, *a*=6.0425(4), *b*=25.3929(13), *c*=9.6370(6) Å, β=97.5785(16)°, *V*=1465.75(15) $Å^3$, *Z*=4, *T*=150(2) K, ρ_{calcd}=1.433 g cm^{-3}; reflections collected/unique 16,084/3519 (R_{int}=0.0212); final *R* indices R_1=0.0286 [$I>2\sigma(I)$], wR_2=0.0767 (all data); data/restraints/parameters=3519/0/232, GoF=1.127, residuals min/max=−0.239/0.273 e $Å^{-3}$.

*4.3.11. Preparation of 3-(2,2-dichlorobutanoyl)-2-(Z)-benzyliden-1,3-thiazinane (**11b**).* Following the procedure used to acylate Boc-**16a**, 2-benzyl-5,6-dihydro-4*H*-[1,3]thiazine (**19b**) (5.0 mmol, 0.96 g)

was treated with TEA (10.0 mmol, 1.4 mL) and 2,2-dichlorobutanoyl chloride (7.5 mmol, 1.32 g) in anhydrous DCM (4+1.5 mL). The raw material, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 99:1 to 90:10). The enamide **11b** was isolated as a light yellow wax (1.49 g, 90%), mixture of rotamers [HRMS found 330.0475. $C_{15}H_{18}Cl_2NOS$ $(M+H)^+$ requires 330.0481]; R_f (20% PE/Et_2O) 0.67; ν_{max} (film) 1654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1 Hz, CH_2CH_3), 2.17 (2H, quintet, *J* 6.0 Hz, CH_2), 2.58 (2H, q, *J* 7.1 Hz, CH_2CH_3), 2.87 (2H, br t, *J* 6.0 Hz, CH_2S), 4.07 (2H, br s, CH_2N), 6.98 (1H, br s, CH=), 7.20–7.60 (5H, m, $5CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) 9.7, 25.5, 28.6, 40.3, 49.0, 85.7, 127.8, 128.1, 129.3, 132.4, 134.4, 164.2.

*4.3.12. Preparation of 3-(2,2-dichloro-3-methylbutanoyl)-2-ethyliden-1,3-thiazinane (**54**).* In a round bottom flask, fitted with a dropping funnel, closed with a $CaCl_2$ tube, 2-ethyl-5,6-dihydro-4*H*-[1,3]thiazine (**53**) (5.0 mmol, 0.646 g), anhydrous DCM (6 mL), and pyridine (6.0 mmol, 0.484 mL) were added. The mixture was thermostated at 0 °C, and a solution of 2,2-dichloro-3-methylbutanoyl chloride (5.5 mmol, 1.042 g) in anhydrous DCM (2 mL) was slowly dropped (30 min) in the flask. The reaction mixture was left under stirring at 25 °C for 24 h. Then, it was diluted with $NaOH_{aq}$ 0.5 M (8 mL) and extracted with DCM (2×5 mL). The combined organic phases were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 90:10). The enamide **54** was isolated as a white solid (1.115 g, 79%), mixture of rotamers [HRMS found 282.0481. $C_{11}H_{18}Cl_2NOS$ $(M+H)^+$ requires 282.0486]; R_f (90% PE/Et_2O) 0.26, mp 66–69 °C; ν_{max} (KBr) 1636 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.15 (6H, d, *J* 6.4, $CH(CH_3)_2$), 1.83 (3H, d, *J* 7.0 Hz, $=CHCH_3$), 2.07 (2H, br m, CH_2), 2.85 (2H, br t, SCH_2), 2.95 (1H, ep, *J* 6.4, $CH(CH_3)_2$), 3.98 (2H, br s, NCH_2), 6.09 (1H, br q, *J* 6.9 Hz, CH=); δ_C (50.31 MHz, $CDCl_3$) 14.4, 18.4, 26.3, 29.4, 41.3, 49.8, 90.9, 130.0, 132.8, 163.9; *m*/*z* (EI, 70 eV) 281 (1, M^+), 246 (37), 156 (100), 128 (71), 101 (50%).

*4.3.13. Preparation of 3-(2,2-dichlorophenylacetyl)-2-ethyliden-1,3-thiazinane (**55**).* Following the procedure used to prepare **54**, 2-ethyl-5,6-dihydro-4*H*-1,3-thiazine (**53**) (5.0 mmol, 0.646 g), was reacted with pyridine (6.0 mmol, 0.484 mL) and 2,2-dichloro-2-phenylacetyl chloride (5.5 mmol, 1.229 g) in anhydrous DCM (6+2 mL). The crude reaction product was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 90:10). This gave the enamide **55** (1.154 g, 73%), as a white/yellowish solid, mixture of rotamers [HRMS found 316.0333. $C_{14}H_{16}Cl_2NOS$ $(M+H)^+$ requires 316.0330]; R_f (90% PE/Et_2O) 0.10, mp 92–94 °C; ν_{max} (KBr) 1669 cm^{-1}; δ_H (200 MHz, acetone-d_6) 1.56 (3H, br d, *J* 6.4 Hz, $=CHCH_3$), 1.86 (2H, br m, CH_2), 2.80 (2H, br t, SCH_2), 3.60 (2H, br s, NCH_2), 5.30 (1H, br s CH=), 7.38–7.70 (5H, m, $5CH_{Ar}$); δ_C (50.31 MHz, $CDCl_3$) 14.3, 25.8, 29.4, 49.9, 88.1, 125.5, 128.6, 129.4, 131.3, 140.4, 162.9; *m*/*z* (EI, 70 eV) 243 (100), 210 (33), 144 (37), 115 (18), 104 (68%).

*4.3.14. Preparation of 3-(trichloroacetyl)-2-ethyliden-1,3-thiazinane (**56**).* Following the protocol used to prepare **54**, 2-ethyl-5,6-dihydro-4*H*-1,3-thiazine (**53**) (5.0 mmol, 0.646 g), was reacted with pyridine (6.0 mmol, 0.484 mL) and trichloroacetyl chloride (5.5 mmol, 1.000 g) in anhydrous DCM (6+2 mL). The crude reaction product was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (100:0 to 90:10). This gave the enamide **56** (0.865 g, 63%), as a orange/brown oil, mixture of rotamers [HRMS found 273.9635. $C_8H_{11}Cl_3NOS$ $(M+H)^+$ requires 273,9627]; R_f (95% PE/Et_2O) 0.26; ν_{max} (KBr) 1679 cm^{-1}; δ_H (200 MHz, acetone-d_6) 1.84 (3H, d, *J* 7.0 Hz, $=CHCH_3$), 2.11 (2H, br m, CH_2), 2.88 (2H, br t, SCH_2), 3.96 (2H, br s, NCH_2), 6.17 (1H, br q, *J* 6.8 Hz, CH=); δ_C (50.31 MHz, $CDCl_3$) 14.5, 26.2, 26.6, 51.0, 92.9, 131.9, 132.7, 159.2; *m*/*z* (EI, 70 eV) 273 (1, M^+), 238 (1), 156 (39), 128 (100), 101 (37%).

*4.3.15. Preparation of 3-(dichlorophenylacetyl)-2-(Z)-benzyliden-1,3-thiazinane (**57**).* Following the procedure used to prepare **54**, 2-phenylmethyl-5,6-dihydro-4*H*-1,3-thiazine (**53**) (5.0 mmol, 0.956 g), was reacted with pyridine (12.0 mmol, 0.968 mL) and 2,2-dichloro-2-phenylacetyl chloride (6.5 mmol, 1.453 g) in anhydrous DCM (6+2 mL). The crude reaction product was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 70:30). This gave the enamide **57** (1.381 g, 73%) as a white/yellowish solid, mixture of rotamers [HRMS found 378.0492. $C_{19}H_{18}Cl_2NOS$ $(M+H)^+$ requires 378.0486]; R_f (70% PE/Et_2O) 0.24, mp 80–82 °C; ν_{max} (KBr) 1653 cm^{-1}; δ_H (200 MHz, acetone-d_6) 2.05 (2H, br s, CH_2), 2.80 (2H, br t, SCH_2), 3.80 (2H, br s, NCH_2), 6.09 (1H, br s CH=), 7.05–7.70 (10H, m, 10 CH_{Ar}); δ_C (50.31 MHz, $CDCl_3$) 25.1, 28.5, 49.2, 88.3, 125.7, 127.9, 128.0, 128.7, 129.3, 129.4, 132.8, 134.0, 140.3, 163.7; *m*/*z* (EI, 70 eV) 307 (100), 278 (30), 236 (6), 204 (7), 175 (22), 118 (23), 91 (20%). A clean sample of **57** was obtained by crystallization from toluene/hexane at 20–25 °C. Selected crystallographic data: $C_{19}H_{17}Cl_2NOS$, *M*=378.30, triclinic, space group *P*-1, *a*=8.9311(2), *b*=9.7317(3), *c*=10.3723(3) Å, *α*=89.8913(11), *β*=88.3043(11), *γ*=76.9034(9)°, *V*=877.66(4) $Å^3$, *Z*=2, *T*=298(2) K, ρ_{calcd}=1.431 g cm^{-3}; reflections collected/unique 22,324/5124 (R_{int}=0.0236); final *R* indices R_1=0.0384 [$I>2\sigma(I)$], wR_2=0.1089 (all data); data/restraints/parameters=5124/3/290, GoF=1.105, residuals min/max=−0.438/0.326 e $Å^{-3}$. Two carbon atoms in the 1,3-thiazinane rings (C5 and C6) were found disordered over two positions, with 90:10 relative occupancies. As a consequence, the crystal is described as a 90:10 mixture of twisted-boat and chair conformers.

4.4. Radical cyclization of *N*-α-perchloroacyl ketene-*N*,X-acetals

*4.4.1. Reaction of 3-(2,2-dichlorobutanoyl)-1-(tert-butyloxycarbonyl)-2-ethylidenimidazolidine (Boc-**10a**).* CuCl (0.6 mmol, 0.060 g), K_2CO_3 (2 mmol, 0.276 g), and the substrate Boc-**10a** (2 mmol, 0.675 g, dr 91:9) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.66 mmol, 138 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 0:100) gave unreacted Boc-**10a** (0.020 g, 3%), Boc-**20a** (80 mg, 11%) as a pale yellow oil, and the *tert*-butyl-*N*-acryloyl-*N*-[2-(2-chlorobutanamido)ethyl]carbamate Boc-**21** (310 mg, 49%) as a pale yellow oil [HRMS found 341.1224. $C_{14}H_{23}ClN_2NaO_4$ $(M+Na)^+$ requires 341.1239]; R_f (40% PE/Et_2O) 0.25; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$), 1.70–1.85 (1H, m, $CHHCH_3$), 1.85–2.00 (1H, m, $CHHCH_3$), 3.35 (2H, q, *J* 5.7 Hz, $NHCH_2$), 3.76 (1H, dt, *J* 14.0, 5.7 Hz, NCHH), 3.80 (1H, dt, *J* 14.0, 5.7 Hz, NCHH), 4.11 (1H, dd, *J* 7.6, 4.4 Hz, CHCl), 5.56 (1H, dd, *J* 10.4, 1.3, =CHH), 6.16 (1H, dd, *J* 16.9, 1.3, =CHH), 6.85 (1H, dd, *J* 16.9, 10.4 Hz, CH=), 7.09 (1H, br m, NH); δ_C (100.62 MHz, $CDCl_3$) 10.0, 27.6, 28.5, 39.0, 43.0, 61.9, 83.8, 127.8, 130.9, 152.3, 168.96, 168.98; *m*/*z* (EI, 70 eV) 226 [16 $(M-HCl-56)^+$], 209 (30), 181 (18), 165 (54), 153 (62), 57 (100%).

*4.4.2. Reaction of 3-(2,2-dichlorobutanoyl)-1-acetyl-2-ethylidenimidazolidine (Ac-**10a**).* CuCl (0.6 mmol, 0.059 g), K_2CO_3 (2 mmol, 0.276 g), and the substrate Ac-**10a** (2 mmol, 0.565 g—mixture 78:22 with its hydrolysis adduct Ac-**20a**) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.66 mmol, 138 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with

a PE/Et_2O gradient (from 90:10 to 40:60) gave Ac-**20a** (0.178 g, 30%—after subtraction of the starting Ac-**20a**) as a yellow oil, and *N*-(2-(*N*-acetylacrylamido)ethyl)-2-chlorobutanamide Ac-**21** (0.052 g, 12%) as a yellow oil [HRMS found 261.0992. $C_{11}H_{18}ClN_2O_3$ $[M+H]^+$ requires 261.1000], R_f (33% PE/Et_2O) 0.12; ν_{max} (film) 1685 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.80–2.20 (2H, m, CH_2CH_3), 2.43 (3H, s, CH_3C=O), 3.35–3.55 (2H, m, $NHCH_2$), 3.87 (2H, t, *J* 6.6 Hz, NCH_2), 4.23 (1H, dd, *J* 7.7, 4.5 Hz, CHCl), 5.82 (1H, dd, *J* 10.3, 1.7 Hz, =CHH), 6.41 (1H, dd, *J* 16.8, 1.7 Hz, =CHH), 6.78 (1H, dd, *J* 16.8, 10.3 Hz, CH=), 7.06 (1H, br s, NH); δ_C (50.32 MHz, $CDCl_3$) 10.2, 26.1, 28.7, 39.1, 43.2, 62.2 (CHCl), 130.0 (CH=), 130.9 (=CH_2), 169.7 (C=O), 173.7 (C=O); *m*/*z* (EI, 70 eV) 260 (5, M^+), 241 (7), 181 (36), 169 (24), 141 (29), 129 (82), 116 (67), 98 (99), 87 (65), 57 (100%).

*4.4.3. Cyclization of 1-(tert-butyloxycarbonyl)-3-(2,2-dichlorobutanoyl)-2-ethyliden-1,3-diazinane (Boc-**10b**).* CuCl (0.6 mmol, 0.060 g), K_2CO_3 (2 mmol, 0.276 g), and the substrate Boc-**10b** (2 mmol, 0.703 g, dr 60:40) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.66 mmol, 138 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 90:10 to 50:50) gave Boc-**29** (0.340 g, 57%), as a pale yellow oil [HRMS found 319.1628. $C_{15}H_{24}N_2NaO_4$ $(M+Na)^+$ requires 319.1628], R_f (50% PE/Et_2O) 0.20, and Boc-**30** (0.080 g, 13%), as a pale yellow oil, mixture of two diastereomers (dr 74:26) [HRMS found 321.1784. $C_{15}H_{26}N_2NaO_4$ $(M+Na)^+$ requires 321.1785], R_f (50% PE/Et_2O) 0.10.

*4.4.3.1. 1-[3-(tert-Butyloxycarbonylamino)propyl]-3-ethyl-4-methyl-2,5-dihydro-1H-pyrrol-2,5-dione (Boc-**29**).* ν_{max} (film) 1702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.6, CH_2CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.72 (2H, quintet, *J* 6.4 Hz, $CH_2CH_2CH_2$), 1.96 (3H, s, CH_3), 2.40 (2H, q, *J* 7.6 Hz, CH_2CH_3), 3.06 (2H, br t, *J* 6.4 Hz, $CH_2CH_2CH_2$), 3.53 (2H, t, *J* 6.4 Hz, $CH_2CH_2CH_2$), 4.97 (1H, br s, NH); δ_C (100.62 MHz, $CDCl_3$) 8.5, 12.6, 17.1, 28.4, 28.9, 34.9, 37.5, 79.2, 136.5, 142.2, 155.9, 172.1, 172.5; *m*/*z* (EI, 70 eV) 296 (1, M^+), 240 (17), 223 (26), 195 (27), 180 (34), 167 (19), 152 (69), 141 (98), 57 (100%).

*4.4.3.2. 1-[3-(tert-Butyloxycarbonylamino)propyl]-3-ethyl-4-methyl-pyrrolidin-2,5-dione (Boc-**30**).* ν_{max} (film) 1699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *major isomer* 1.02 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.21 (3H, d, *J* 7.9 Hz, $CHCH_3$), 1.40 (9H, s, $C(CH_3)_3$), 1.55–1.80 (4H, m, $CH_2CH_2CH_2$+CH_2CH_3), 2.70 (1H, dt, *J* 7.9, 6.4 Hz, C(3)H), 2.92 (1H, quintet, *J* 7.9 Hz, C(4)H), 3.02 (2H, br q, *J* 6.4 Hz, $NHCH_2$), 3.52 (2H, t, *J* 6.4 Hz, NCH_2), 5.04 (1H, br s, NH), *minor isomer* 0.98 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.31 (3H, d, *J* 7.3 Hz, $CHCH_3$), 1.40 (9H, s, $C(CH_3)_3$), 1.55–1.80 (3H, m, $CH_2CH_2CH_2$+$CHHCH_3$), 1.80–1.95 (1H, m, $CHHCH_3$), 2.30 (1H, dt, *J* 8.3, 5.0 Hz, C(3)H), 2.47 (1H, dq, *J* 7.3, 5.0 Hz, C(4)H), 3.02 (2H, br q, *J* 6.4, $NHCH_2$), 3.52 (2H, t, *J* 6.4 Hz, NCH_2), 5.04 (1H, br s, NH); δ_C (100.62 MHz, $CDCl_3$) *major isomer* 11.4, 12.3, 19.7, 28.0, 28.3, 35.6, 37.2, 38.1, 44.9, 79.1, 155.1 (C=O), 179.7 (C=O), 180.7 (C=O), *minor isomer* 10.9, 16.3, 23.5, 28.0, 28.3, 35.6, 37.2, 40.2, 49.2, 79.1, 155.1 (C=O), 179.2 (C=O), 180.1 (C=O); *m*/*z* (EI, 70 eV) *major isomer* 242 [48 $(M-56)^+$], 225 (25), 197 (18), 182 (44), 155 (99), 141 (56), 57 (100%), *minor isomer* 242 [48 $(M-56)^+$], 225 (24), 197 (20), 182 (48), 155 (100), 141 (56), 57 (99%).

*4.4.4. Cyclization of 1-acetyl-3-(2,2-dichlorobutanoyl)-2-ethyliden-1,3-diazinane (Ac-**10b**).* CuCl (0.6 mmol, 0.060 g), K_2CO_3 (2 mmol, 0.276 g), and the substrate Ac-**10b** (2 mmol, 0.586 g, *Z*/*E* 64:36) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.66 mmol, 138 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 90:10 to 10:90) gave unreacted Ac-**10b** (0.129 g, 22%), Ac-**29** (0.267 g, 56%), as a yellow oil [HRMS found 239.1392. $C_{12}H_{19}N_2O_3$ $(M+H)^+$ requires 239.1390], R_f (10% PE/Et_2O) 0.06, and Ac-**30** (0.034 g, 7%), as a yellow-orange oil, mixture of two diastereomers (dr 86:14) [HRMS found 241.1552. $C_{12}H_{21}N_2O_3$ $[M+H]^+$ requires 241.1547], R_f (10% PE/Et_2O) 0.04.

*4.4.4.1. 1-[3-(Acetylamino)propyl]-3-ethyl-4-methyl-2,5-dihydro-1H-pyrrol-2,5-dione (Ac-**29**).* ν_{max} (film) 1709, 1655 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.71 (2H, quintet, *J* 6.3 Hz, $CH_2CH_2CH_2$), 1.93 (3H, s, $C(4)CH_3$), 1.98 (3H, s, CH_3C=O), 2.36 (2H, q, *J* 7.6 Hz, CH_2CH_3), 3.14 (2H, q, *J* 6.3, $NHCH_2$), 3.49 (2H, t, *J* 6.3 Hz, NCH_2), 6.61 (1H, br s, NH); δ_C (100.62 MHz, $CDCl_3$) 8.4, 12.5, 17.0, 23.0, 28.2 (CH_2), 34.7, 36.2, 136.5, 142.2, 170.5, 172.1, 172.5; *m*/*z* (EI, 70 eV) 238 (53, M^+), 195 (44), 179 (55), 166 (37), 152 (100), 141 (56), 73 (81), 56 (76%).

*4.4.4.2. 1-[3-(Acetylamino)propyl]-3-ethyl-4-methyl-pyrrolidin-2,5-dione (Ac-**30**).* ν_{max} (film) 1700, 1658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *major isomer* 1.03 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.22 (3H, d, *J* 7.7 Hz, $C(4)CH_3$), 1.50–1.80 (4H, m, CH_2CH_3+$CH_2CH_2CH_2$), 2.00 (3H, s, CH_3C=O), 2.73 (1H, q, *J* 7.6 Hz, C(3)H), 2.95 (1H, quintet, *J* 7.7 Hz, C(4)H), 3.14 (2H, br s, $NHCH_2$), 3.52 (2H, t, *J* 6.4 Hz, NCH_2), 6.64 (1H, br s, NH), *minor isomer* 0.99 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.32 (3H, d, *J* 7.2 Hz, $C(4)CH_3$), 1.55–1.95 (4H, m, CH_2CH_3+$CH_2CH_2CH_2$), 2.00 (3H, s, CH_3C=O), 2.25–2.40 (1H, m, C(3)H), 2.45–2.55 (1H, m, C(4)H), 3.14 (2H, br s, $NHCH_2$), 3.52 (2H, t, *J* 6.4 Hz, NCH_2), 6.64 (1H, br s, NH); δ_C (100.62 MHz, $CDCl_3$) *major isomer* 11.4, 12.3, 19.7, 23.0, 27.3, 35.4, 36.1, 38.1, 44.9, 170.6, 179.9, 180.9, *minor isomer* 10.1, 16.3, 23.0, 23.5, 27.3, 35.6, 36.0, 40.3, 49.2, 170.6, 179.4, 180.3; *m*/*z* (EI, 70 eV) *major isomer* 240 (13, M^+), 197 (45), 141 (32), 86 (64), 73 (30), 56 (100%), *minor isomer* 240 (13, M^+), 197 (42), 149 (71), 141 (30), 86 (61), 73 (28), 56 (100%).

*4.4.5. Cyclization of (Z)-3-(2,2-dichlorobutanoyl)-1-acetyl-2-benzylidenimidazolidine (**13a**).* CuCl (0.1 mmol, 0.010 g), K_2CO_3 (2 mmol, 0.280 g), and the substrate **13a** (2 mmol, 0.682 g) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.11 mmol, 24 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a DCM/Et_2O gradient (from 0:100 to 40:60) gave the 1-acetyl-6,11a-epoxy-6-ethyl-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]imidazo[1,2-*a*]azepin-5(6*H*)-one **24** (0.554 g, 97%) as a white flake solid, mixture of rotamers (60:40) [HRMS found 309.1216. $C_{16}H_{18}N_2NaO_3$ $(M+Na)^+$ requires 309.1210], R_f (50% DCM/Et_2O) 0.23; mp 143.6–144.2 °C; ν_{max} (KBr) 1732, 1682, 1668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) *major rotamer* 1.03 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.10–2.40 (2H, m, CH_2CH_3), 2.33 (3H, s, CH_3C=O), 3.07 (1H, d, *J* 16.4 Hz, CHHPh), 3.20–3.40 (1H, m, $CHHCH_2N$), 3.80–4.10 (4H, m, CH*H*Ph+CH*HCH*$_2$N), 7.10–7.40 (4H, m, $4CH_{Ar}$); *minor rotamer* 1.03 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.10–2.40 (2H, m, CH_2CH_3), 2.20 (3H, s, CH_3C=O), 2.85 (1H, d, *J* 16.0 Hz, CHHPh), 3.20–3.40 (1H, m, $CHHCH_2N$), 3.80–4.10 (3H, m, CH*HCH*$_2$N), 4.69 (1H, d, *J* 16.0, CHHPh), 7.10–7.40 (4H, m, $4CH_{Ar}$); δ_C (100.62 MHz, $CDCl_3$) *major rotamer* 7.2, 22.6, 23.0, 37.1, 37.5, 47.4, 90.2, 101.7, 124.0, 126.9, 128.4, 129.3, 133.3, 134.5, 169.3, 173.7; *minor rotamer* 7.2, 23.0, 24.2, 35.2, 39.8, 48.4, 88.8, 103.3, 123.7, 126.3, 128.2, 129.3, 134.3, 169.7, 175.3; *m*/*z* (EI, 70 eV) 286 (5, M^+), 243 (10), 229 (100), 187 (66), 161 (36), 43 (29%). A sample of **24**, suitable for the single-crystal X-ray diffraction, was obtained by crystallization, under Argon, from DCM/hexane at 4 °C. Selected crystallographic data: $C_{16}H_{18}N_2O_3$, *M*=286.32, monoclinic, space group $P2_1/c$, *a*=9.3270(3),

b=29.0321(11), c=10.7640(4) Å, β=91.3073(11)°, V=2913.94(18) Å^3, Z=8, T=298(2) K, ρ_{calcd}=1.305 g cm^{-3}; reflections collected/unique 38,535/8476 (R_{int}=0.0257); final R indices R_1=0.0421 [$I>2\sigma(I)$], wR_2=0.1249 (all data); data/restraints/parameters=8476/0/383, GoF=1.044, residuals min/max=−0.203/0.243 e Å^{-3}.

*4.4.6. Cyclization of 1-acetyl-3-(2,2-dichlorobutanoyl)-2-benzyliden-1,3-diazinane (**13b**).* CuCl (0.6 mmol, 0.060 g), K_2CO_3 (2 mmol, 0.276 g), and the substrate **13b** (2 mmol, 0.711 g, *Z*/*E* 57:43) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and PMDETA (0.66 mmol, 138 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 90:10 to 0:100) gave the 1-(3-acetylamidopropyl)-3-ethyl-4-phenyl-2,5-dihydro-1*H*-pyrrol-2,5-dione **31** (0.355 g, 59%), as a yellow oil [HRMS found 301.1554. $C_{17}H_{21}N_2O_3$ (M+H)$^+$ requires 301.1547]; R_f (95% DCM/MeOH) 0.45; ν_{max} (film) 1703, 1652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.5 Hz, CH_2CH_3), 1.78 (2H, quintet, *J* 6.3 Hz, $CH_2CH_2CH_2$), 1.94 (3H, s, CH_3C=O), 2.55 (2H, q, *J* 7.5 Hz, CH_2CH_3), 3.19 (2H, q, *J* 6.3, CH_2NH), 3.57 (2H, t, *J* 6.3 Hz, NCH_2), 6.88 (1H, br s, NH), 7.30–7.55 (5H, m, 5CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 12.6, 17.2, 22.6, 27.9, 34.9, 36.0, 128.1, 128.3, 128.8, 129.1, 136.4, 141.4, 170.0, 170.8, 171.2; *m*/*z* (EI, 70 eV) 300 (100, M$^+$), 258 (7), 241 (70), 228 (40), 214 (19), 203 (46), 129 (54), 115 (63), 73 (99%).

*4.4.7. Cyclization of 3-(2,2-dichlorobutanoyl)-2-(Z)-benzylidenthiazolidine (**11a**).* CuCl (0.2 mmol, 0.020 g), Na_2CO_3 (2 mmol, 0.212 g), and the substrate **11a** (2 mmol, 0.633 g) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and TMEDA (0.4 mmol, 58 μL) were added under argon. The mixture was stirred at 30 °C and after 16 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 0:100) gave **38a** (0.135, 26%) as a yellow oil [HRMS found 521.1566. $C_{28}H_{29}N_2O_4S_2$ (M+H)$^+$ requires 521.1563], R_f (20% PE/Et_2O) 0.70, **39a** (0.242, 48%) as a yellow oil [HRMS found 522.1878. $C_{28}H_{32}N_3O_3S_2$ (M+NH_4)$^+$ requires 522.1880], R_f (20% PE/Et_2O) 0.44, and an unseparable mixture of *dl*-**40**, *meso*-**40**, and **41** [68:20:12 (^{1}H NMR)] as a yellow foamy solid (0.078 g, 16%; 0.023 g, 5%; 0.015 g, 3%), R_f (20% PE/Et_2O) 0.19. Some *dl*-**40** was separated by crystallization from a solution of DCM/*n*-hexane, as a yellow solid [HRMS found 511.1484. $C_{28}H_{28}N_2NaO_2S_2$ (M+Na)$^+$ requires 511.1484], mp 175–177 °C.

*4.4.7.1. 1,1′-[2,2′-Disulfanediylbis(ethane-2,1-diyl)]bis(3-ethyl-4-phenyl-1H-pyrrole-2,5-dione) (**38a**).* ν_{max} (film) 1699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22 (6H, t, *J* 7.5 Hz, $2CH_2CH_3$), 2.61 (4H, q, *J* 7.5 Hz, $2CH_2CH_3$), 2.99 (4H, t, *J* 6.8 Hz, $2CH_2$), 3.91 (4H, t, *J* 6.8 Hz, $2CH_2$), 7.20–7.60 (10H, m, 10CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 12.9, 17.5, 35.7, 36.9, 128.3, 128.6, 129.1, 129.4, 136.7, 141.7, 170.5, 171.0.

*4.4.7.2. 3-Ethyl-1-[2-(6-ethyl-5-oxo-7-phenyl-2,3,5,7a-tetrahydropyrrolo[2,1-b]thiazol-7a-ylthio)ethyl]-4-phenyl-1H-pyrrole-2,5-dione (**39a**).* ν_{max} (film) 1702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.22 (3H, t, *J* 7.6, CH_2CH_3), 2.35–2.52 (4H, m, CH_2CH_3+CH_2), 2.58 (2H, q, *J* 7.6, CH_2CH_3), 3.35–3.52 (2H, m, CH_2), 3.56 (2H, t, *J* 7.0, CH_2), 3.55–3.66 (1H, m, CH*H*), 4.34 (1H, ddd, *J* 11.5, 7.7, 3.5, C*H*H), 7.30–7.60 (10H, m, 10CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 13.0, 13.1, 17.6, 18.1, 30.8, 37.3, 38.3, 42.2, 85.2, 128.2, 128.5, 128.6, 128.7, 129.2, 129.3, 129.5, 131.4, 135.5, 136.7, 141.8, 153.4, 170.4, 170.9, 172.0.

*4.4.7.3. (±)-(7aR,7′aR)-6,6′-Diethyl-7,7′-diphenyl-2H,2′H-7a,7′a-bipyrrolo[2,1-b]thiazole-5,5′(3H,3′H)-dione (dl-**40**).* ν_{max} (KBr) 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.98 (6H, t, *J* 7.3 Hz, $2CH_2CH_3$), 2.06 (2H, dq, *J* 14.3, 7.3 Hz, 2C*H*HCH_3), 2.20 (2H, dq, *J* 14.3, 7.3 Hz, 2CH*H*CH_3), 3.35 (2H, q, *J* 8.4 Hz, 2C*H*HCH_2), 3.56 (2H, dt, *J* 8.4, 2.7 Hz, 2CH*H*CH_2), 3.67 (2H, dt, *J* 11.5, 8.4 Hz, $2CH_2CHH$), 4.16 (2H, ddd, *J* 11.5, 8.4, 2.7 Hz, $2CH_2CHH$), 7.32–7.48 (10H, m, 10CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 12.8, 17.7, 38.6, 44.3, 87.7 (2NCS), 127.9, 128.0, 129.1, 132.9, 134.6, 156.2, 173.6; *m*/*z* (ESI) 999.0 (2M+Na)$^+$, 511.1 (M+Na)$^+$, 244.2 (M/2)$^+$. Selected crystallographic data: $C_{28}H_{28}N_2O_2S_2$, M=488.64, orthorhombic, space group *Pccn*, a=30.2370(7), b=17.4914(5), c=18.6559(5) Å, V=9866.9(4) Å^3, Z=16, T=298(2) K, ρ_{calcd}=1.316 g cm^{-3}; reflections collected/unique 112,644/11,330 (R_{int}=0.0405); final R indices R_1=0.0481 [$I>2\sigma(I)$], wR_2=0.1372 (all data); data/restraints/parameters 11,330/0/613, GoF=1.020, residuals min/max=−0.284/0.313 e Å^{-3}.

*4.4.7.4. meso-(7aR,7′aS)-6,6′-Diethyl-7,7′-diphenyl-2H,2′H-7a,7′a-bipyrrolo[2,1-b]-1,3-thiazole-5,5′(3H,3′H)-dione (meso-**40**).* δ_H (400 MHz, $CDCl_3$) 0.81 (6H, t, *J* 7.2 Hz, $2CH_2CH_3$), 1.86 (2H, dq, *J* 14.1, 7.2 Hz, 2×C*H*HCH_3), 1.97 (2H, dq, *J* 14.1, 7.2 Hz, 2×CH*H*CH_3), 3.10–3.25 (4H, m, 2×CH_2CH_2), 3.65–3.85 (2H, m, 2×CH_2CHH), 4.47 (2H, ddd, *J* 11.5, 7.5, 2.3 Hz, 2×CH_2CHH), 6.95–7.70 (10H, m, 10×CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 12.8, 17.4, 36.8, 47.0, 88.6, 127.6, 128.5, 129.7, 132.6, 136.3, 156.2, 175.2; *m*/*z* (ESI) 999.0 (2M+Na)$^+$, 511.1 (M+Na)$^+$, 244.1 (M/2)$^+$.

*4.4.7.5. 7a,7a′-Oxybis{6-ethyl-7-phenyl-2,3-dihydropyrrolo[2,1-b]thiazol-5(7aH)-one} (**41**).* δ_H (400 MHz, $CDCl_3$) 1.19 (6H, t, *J* 7.6 Hz, 2×CH_2CH_3), 2.55–2.70 (4H, m, 2×CH_2CH_3), 2.95–3.05 (4H, m, 2×CH_2), 3.85–3.95 (4H, m, 2×CH_2), 6.95–7.70 (10H, m, 10×CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) (only identified signals are reported) 13.0, 17.7, 35.9, 37.8, 128.6, 128.9, 129.3, 141.9; *m*/*z* (ESI) 1031.4 (2M+Na)$^+$, 527.2 (M+Na)$^+$.

*4.4.8. Cyclization of 3-(2,2-dichlorobutanoyl)-2-(Z)-benzyliden-1,3-thiazinane (**11b**).* CuCl (0.1 mmol, 0.010 g), Na_2CO_3 (2 mmol, 0.212 g), and the substrate **11b** (2 mmol, 0.661 g) were weighed into an oven dried Schlenk tube, then anhydrous CH_3CN (3 mL) and TMEDA (0.2 mmol, 30 μL) were added under argon. The mixture was stirred at 30 °C and after 17 h diluted with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under vacuum. Chromatography of the recovered material on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80) gave the dimer **38b** (0.127 g, 23%) as a yellow oil [HRMS found 571.1709. $C_{30}H_{32}N_2NaO_4S_2$ (M+Na)$^+$ requires 571.1696], R_f (20% PE/Et_2O) 0.67, and the thioacetal **39b** (0.331 g, 62%) as a yellow oil [HRMS found 555.1744. $C_{30}H_{32}N_2NaO_3S_2$ (M+Na)$^+$ requires 555.1747], R_f (20% PE/Et_2O) 0.45.

*4.4.8.1. 1,1′-[3,3′-Disulfanediylbis(propane-3,1-diyl)]bis(3-ethyl-4-phenyl-1H-pyrrole-2,5-dione) (**38b**).* ν_{max} (film) 1701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.4 Hz, 2×CH_2CH_3), 2.04 (4H, quintet, *J* 7.1 Hz, 2×CH_2), 2.61 (4H, q, *J* 7.4 Hz, 2×CH_2CH_3), 2.71 (4H, t, *J* 7.1 Hz, 2×CH_2), 3.68 (4H, t, *J* 7.1 Hz, 2×CH_2), 7.35–7.60 (10H, m, 10×CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 13.1, 17.7, 28.1, 36.0, 36.9, 128.6, 128.8, 129.3, 129.5, 136.9, 141.9, 171.0, 171.5.

*4.4.8.2. 3-Ethyl-1-{3-(7-ethyl-6-oxo-8-phenyl-3,4,6,8a-tetrahydro-2H-pyrrolo[2,1-b]-1,3-thiazin-8a-ylthio)propyl}-4-phenyl-1H-pyrrole-2,5-dione (**39b**).* ν_{max} (film) 1704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.5 Hz, CH_2CH_3), 1.18 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.59 (1H, br q, *J* 13.0, $CH_2CH_{ax}HCH_2$), 1.76 (2H, quintet, *J* 6.9 Hz, $CH_2CH_2CH_2$), 1.85–2.00 (2H, m, C*H*HS+$CH_2CH_{eq}HCH_2$), 2.00–2.13 (1H, m, CH*H*S), 2.32 (2H, m, CH_2CH_3), 2.55 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.55–2.65 (1H, m, $CH_{eq}HS$), 3.13 (1H, dt, *J* 13.0, 2.4 Hz, $CH_{ax}HN$), 3.28 (1H, br t, *J* 13.0 Hz, $CH_{ax}HS$), 3.40–3.60 (2H, m, CH_2N), 4.33 (1H, br d, *J* 13.0 Hz, $CH_{eq}HN$), 7.20–7.60 (10H, m, 10×CH_{Ar}); δ_C (100.62 MHz, $CDCl_3$) 12.8, 13.2, 17.4, 17.7, 25.3, 26.3, 27.3, 27.8, 35.4,

37.0, 74.0 (SCN), 128.0, 128.2, 128.5, 128.7, 128.8, 129.0, 129.2, 131.1, 136.55, 136.60, 141.6, 151.6, 166.7, 170.5, 171.0.

*4.4.9. Cyclization of 3-(2,2-dichloro-3-methylbutanoyl)-2-(Z)-ethyliden[1,3]thiazinane (**54**).* Following the procedure used for the cyclization of **11b**, the enamide **54** (2 mmol, 0.757 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude extract on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the disulfide **58** (0.086 g, 19%) as a colorless oil [HRMS found 453.1879. $C_{22}H_{33}N_2O_4S_2$ $(M+H)^+$ requires 453.1876], R_f (50% PE/Et_2O) 0.49, and the thioacetal **59** (0.319 g, 73%) as a yellow oil [HRMS found 437.1937. $C_{22}H_{33}N_2O_3S_2$ $(M+H)^+$ requires 437.1927], R_f (60% PE/Et_2O) 0.25.

*4.4.9.1. 1,1′-[3,3′-Disulfanediylbis(propane-3,1-diyl)]bis(3-isopropyl-4-methyl-1H-pyrrole-2,5-dione) (**58**).* ν_{max} (film) 1702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (12H, d, *J* 7.0 Hz, 2×CH(CH_3)$_2$), 1.95 (4H, quintet, *J* 7.0 Hz, 2×$CH_2CH_2CH_2$), 1.98 (6H, s, 2×CH_3), 2.64 (4H, t, *J* 7.2 Hz, CH_2S), 2.93 (2H, sept, *J* 7.0 Hz, 2×*CH*(CH_3)$_2$), 3.55 (4H, t, *J* 6.8 Hz, 2×CH_2N); δ_C (50 MHz, $CDCl_3$) 8.6, 20.6, 25.4, 28.2, 36.1, 36.6, 135.4, 145.0, 171.4, 172.2; *m*/*z* (EI, 70 eV) 226 (3, 1/2M^+), 194 (100), 166 (45), 81 (11), 41(9).

*4.4.9.2. 3-Isopropyl-1-{3-(7-isopropyl-8-methyl-6-oxo-3,4,6,8a-tetrahydro-2H-pyrrolo[2,1-b]-1,3-thiazin-8a-ylthio)propyl}-4-methyl-1H-pyrrole-2,5-dione (**59**).* ν_{max} (film) 1768, 1701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.242, 1.245, 1.250, 1.255 (3H each, 4d, *J* 7.0 Hz each, CH(CH_3)$_2$), 1.62 (1H, m, partially overlapped, $CH_2CH_{ax}CH_2$), 1.67 (2H, quintet, *J* 7.2 Hz, $CH_2CH_2CH_2$), 1.86 (2H, m, acyclic CH_2S), 1.98 (3H, s, CH_3), 1.99 (m, 1H, $CH_2CH_{eq}HCH_2$), 2.07 (3H, s, CH_3), 2.71 (dt, 1H, J_{gem} 13.3 Hz, J_{ae}=J_{ee}=3.1 Hz, $CH_{eq}HS$), 2.89, 2.93 (1H each, 2 sept, *J* 7.0 Hz each, *CH*(CH_3)$_2$), 3.08 (1H, dt, J_{aa}=J_{gem}=13.4 Hz, J_{ae} 3.2 Hz, $CH_{ax}HN$), 3.34 (1H, dt, J_{aa}=J_{gem}=13.3, J_{ae} 3.1 Hz, $CH_{ax}HS$), 3.45 (2H, t, *J* 7.2 Hz, acyclic CH_2N), 4.28 (1H, br d, *J* 13.4 Hz, $CH_{eq}HN$); δ_C (125 MHz, $CDCl_3$) 8.6, 10.5, 20.5, 20.6, 20.9, 25.35, 25.45, 26.0, 26.8, 27.7, 27.9, 35.5, 37.0, 73.9, 135.5, 137.5, 145.1, 149.2, 167.2, 171.3, 172.1; *m*/*z* (ESI) 475.4 $(M+K)^+$, 459.5 $(M+Na)^+$, 437.4 $(M+H)^+$.

*4.4.10. Cyclization of 3-(2,2-dichlorophenylacetyl)-2-(Z)-ethyliden-1,3-thiazinane (**55**).* Following the procedure used for the cyclization of **11b**, the enamide **55** (2 mmol, 0.633 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude extract on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the disulfide **60** (0.078 g, 15%) as a thick yellow oil [HRMS found 521.1538. $C_{28}H_{29}N_2O_4S_2$ $(M+H)^+$ requires 521.1563], R_f (50% PE/Et_2O) 0.42, and the thioacetal **61** (0.419 g, 83%) as a yellow solid [HRMS found 505.1600. $C_{28}H_{29}N_2O_3S_2$ $(M+H)^+$ requires 505.1614], R_f (50% PE/Et_2O) 0.18, mp 70–71 °C.

*4.4.10.1. 1,1′-[3,3′-Disulfanediylbis(propane-3,1-diyl)]bis(3-methyl-4-phenyl-1H-pyrrole-2,5-dione) (**60**).* ν_{max} (film) 1767, 1701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.05 (4H, quintet, *J* 7.0 Hz, 2×$CH_2CH_2CH_2$), 2.20 (s, 6H, 2×CH_3), 2.71 (4H, t, *J* 7.0 Hz, 2×CH_2S), 3.69 (4H, t, *J* 7.0 Hz, 2×CH_2N), 7.44, 7.47 (2 m, 6H, 2×*p*- and *m*-CH_{Ar}), 7.58 (dd, 4H, 2×*o*-CH_{Ar}); δ_C (125 MHz, $CDCl_3$) 9.9, 28.1, 36.0, 36.9, 128.5, 128.9, 129.4, 129.5, 136.5, 137.0, 170.9, 171.8; *m*/*z* (ESI) 559.3 $(M+K)^+$, 543.4 $(M+Na)^+$, 521.4 $(M+H)^+$.

*4.4.10.2. 3-Methyl-1-{3-(8-methyl-6-oxo-7-phenyl-3,4,6,8a-tetrahydro-2H-pyrrolo[2,1-b]-1,3-thiazin-8a-ylthio)propyl}-4-phenyl-1H-pyrrole-2,5-dione (**61**).* ν_{max} (film) 1767, 1703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.71 (1H, tq, J_{aa}=J_{gem} 13.5, J_{ae} 3.7 Hz, $CH_2CH_{ax}HCH_2$), 1.79 (2H, quintet, *J* 7.1 Hz, $CH_2CH_2CH_2$), 2.03 (2H, t, *J* 7.1 Hz, acyclic CH_2S), 2.04 (1H, tq, overlapped, $CH_2CH_{eq}HCH_2$), 2.17 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.76 (1H, dt, J_{gem} 13.5, J_{ea}=J_{ee}=2.5 Hz, $CH_{eq}HS$), 3.20 (1H, dt, J_{gem}=J_{aa}=13.4, J_{ae} 3.0 Hz, $CH_{ax}HN$), 3.42 (1H, dt, J_{gem}=J_{aa}=13.5, J_{ae}=2.5 Hz, $CH_{ax}HS$), 3.60 (2H, dt, *J* 6.9, 2.2 Hz, acyclic CH_2N), 4.40 (1H, br d, *J* 13.4 Hz, $CH_{eq}HN$), 7.34 (1H, m, CH_{Ar}), 7.40 (2H, m, CH_{Ar}), 7.46 (3H, m, CH_{Ar}), 7.51 (2H, dd, CH_{Ar}), 7.55 (2H, dd, CH_{Ar}); δ_C (125 MHz, $CDCl_3$) 9.9, 11.7, 26.2, 27.1, 28.0, 28.05, 36.0, 37.3, 74.2, 128.2, 128.3, 128.5, 128.9, 129.3, 129.4, 129.5, 130.6, 131.7, 136.6, 137.1, 152.1, 166.5, 170.9, 171.8; *m*/*z* (ESI) 543.4 $(M+K)^+$, 527.4 $(M+Na)^+$, 505.3 $(M+H)^+$.

*4.4.11. Cyclization of 3-(trichloroacetyl)-2-(Z)-ethyliden-1,3-thiazinane (**56**).* Following the procedure used for the cyclization of **11b**, the enamide **56** (2 mmol, 0.757 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude extract on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the disulfide **62** (0.114 g, 26%) as a white solid [HRMS found 437.0159. $C_{16}H_{19}Cl_2N_2O_4S_2$ $(M+H)^+$ requires 437.0158], R_f (50% PE/Et_2O) 0.36, mp 97–98 °C and the thioacetal **63** (0.122 g, 29%) as a yellow solid [HRMS found 421.0221. $C_{16}H_{19}Cl_2N_2O_3S_2$ $(M+H)^+$ requires 421.0209], R_f (60% PE/Et_2O) 0.20, mp 127–129 °C.

*4.4.11.1. 1,1′-[3,3′-Disulfanediylbis(propane-3,1-diyl)]bis(3-chloro-4-methyl-1H-pyrrole-2,5-dione) (**62**).* ν_{max} (KBr) 1710 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.99 (4H, quintet, *J* 7.0 Hz, 2×$CH_2CH_2CH_2$), 2.06 (6H, s, 2×CH_3), 2.67 (4H, t, *J* 7.2 Hz, 2×CH_2S), 3.65 (4H, t, *J* 7.0 Hz, 2×CH_2N); δ_C (50 MHz, $CDCl_3$) 9.0, 28.0, 35.9, 37.4, 133.8, 137.7, 165.2, 169.0; *m*/*z* (EI, 70 eV) 436 (1, M^+) (1), 218 (2), 186 (100), 158 (91), 56 (14), 41(12).

*4.4.11.2. 3-Chloro-1-{3-(7-chloro-8-methyl-6-oxo-3,4,6,8a-tetrahydro-2H-pyrrolo[2,1-b]-1,3-thiazin-8a-ylthio)propyl}-4-methyl-1H-pyrrole-2,5-dione (**63**).* ν_{max} (KBr) 1756, 1703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.62 (1H, tq, partially overlapped, $CH_2CH_{ax}H$ CH_2), 1.68 (2H, t, *J* 7.1 Hz, acyclic $CH_2CH_2CH_2$), 1.91 (2H, m, *J* 7.1 Hz, acyclic CH_2S), 2.02 (1H, overlapped m, $CH_2CH_{eq}HCH_2$), 2.04 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.71 (1H, dt, J_{gem} 13.4, J_{ea}=J_{ee}=3.4 Hz, $CH_{eq}HS$), 3.13 (1H, dt, J_{gem}=J_{aa}=13.4, J_{ae} 2.9 Hz, $CH_{ax}HN$), 3.32 (1H, dt, J_{gem}=J_{aa}=13.4, J_{ae}=3.4 Hz, $CH_{ax}HS$), 3.51 (2H, t, *J* 7.0 Hz, acyclic CH_2N), 4.29 (1H, br d, *J* 13.4 Hz, $CH_{eq}HN$); δ_C (125 MHz, $CDCl_3$) 9.1, 10.8, 26.0, 26.9, 27.8, 27.9, 36.3, 37.6, 73.7, 125.3, 133.8, 137.8, 151.6, 162.0, 165.1, 169.0; *m*/*z* (ESI) 459.2 $(M+K)^+$, 443.3 $(M+Na)^+$.

*4.4.12. Cyclization of 3-(2,2-dichlorophenylacetyl)-2-(Z)-benzyliden-1,3-thiazinane (**57**).* Following the procedure used for the cyclization of **11b**, the enamide **57** (2 mmol, 0.757 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude extract on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 0:100), the disulfide **64** (0.290 g, 45%) as a yellow solid [HRMS found 645.1909. $C_{38}H_{33}N_2O_4S_2$ $(M+H)^+$ requires 645.1876], R_f (60% PE/Et_2O) 0.50, mp 115–117 °C, and the thioacetal **65** (0.333 g, 53%) as a bright yellow solid [HRMS found 629.1939. $C_{38}H_{33}N_2O_3S_2$ $(M+H)^+$ requires 629.1927], R_f (60% PE/Et_2O) 0.15, mp 105–107 °C.

*4.4.12.1. 1,1′-[3,3′-Disulfanediylbis(propane-3,1-diyl)]bis(3,4-diphenyl-1H-pyrrole-2,5-dione) (**64**).* ν_{max} (film) 1762, 1700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.11 (4H, quintet, *J* 7.0 Hz, 2×$CH_2CH_2CH_2$), 2.77 (4H, t, *J* 7.0 Hz, 2×CH_2S), 3.77 (4H, t, *J* 7.0 Hz, 2×CH_2N), 7.36 (12H, m, 12×CH_{Ar}), 7.54 (8H, dd, 8×CH_{Ar}); δ_C (125 MHz, $CDCl_3$) 28.1, 36.0, 37.2, 128.5, 128.6, 129.8, 129.9, 136.1, 170.7; *m*/*z* (ESI) 667.4 $(M+Na)^+$.

*4.4.12.2. 1-{3-(6-Oxo-7,8-diphenyl-3,4,6,8a-tetrahydro-2H-pyrrolo[2,1-b]-1,3-thiazin-8a-ylthio)propyl}-3,4-diphenyl-1H-pyrrole-2,5-dione (**65**).* ν_{max} (film) 1767, 1701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.76 (1H, qt, J_{gem}=J_{aa}=13.5, J_{ae}=2.7 Hz, $CH_2CH_{ax}HCH_2$), 1.90 (2H, quintet, *J* 7.2 Hz, $CH_2CH_2CH_2$), 2.07 (1H, dt, J_{gem}=J_{aa} 13.5, J_{ee}=J_{ea}=2.7 Hz, $CH_2CH_{eq}HCH_2$), 2.13 (1H, dt, *J* 12.5, 7.2 Hz, acyclic *CH*HS), 2.24 (1H, dt, *J* 12.5, 7.2 Hz, acyclic CH*H*S), 2.72 (1H, dt, J_{gem}

13.5, J_{ea}=J_{ee}=2.7 Hz, CH_{eq}HS), 3.30 (1H, dt, J_{gem}=J_{aa}=13.4, J_{ae} 2.9 Hz,CH_{ax}HN), 3.42 (1H, dt, J_{gem}=J_{aa}=13.4, J_{ae} 2.5 Hz, CH_{ax}HS), 3.66 (2H, m, CH_2N), 4.50 (1H, br d, J 13.4 Hz, CH_{eq}HN), 7.23 (2H, m, CH_{Ar}), 7.27–7.40 (10H, m, CH_{Ar}), 7.43 (6H, m, CH_{Ar}), 7.55 (2H, dd, J 7.9, 1.6 Hz, CH_{Ar}); δ_C (125 MHz, $CDCl_3$) 25.8, 26.9, 27.7, 28.3, 36.0, 37.6, 74.6, 128.2, 128.35, 128.4, 128.5, 129.2, 129.7, 129.8, 129.85, 129.9, 130.5, 131.5, 132.8, 136.2, 152.6, 166.0, 170.6; m/z (ESI) 651.4 $(M+Na)^+$.

4.5. Preparation of disubstituted maleic anhydrides

*4.5.1. Preparation of 3-ethyl-4-phenylfuran-2,5-dione (**52**).* In a Schlenk tube, fitted with a screw cap, a perforable septum and a stirring bar, were weighed 3-(2,2-dichlorobutanoyl)-2-(*Z*)-benzyliden-[1,3]thiazinane (**11b**) (4.5 mmol, 1.485 g), Na_2CO_3 (4.5 mmol, 0.477 g), and CuCl (0.225 mmol, 0.023 g). Anhydrous CH_3CN (6.8 mL) and TMEDA (0.45 mmol, 68 μL) were then added under argon. The stirred reaction mixture was thermostated at 30 °C and, after 16 h, it was diluted with H_2O (20 mL) and extracted with DCM (3×20 mL). The organic phases were collected, dried over $MgSO_4$, filtered, and evaporated in a Schlenk tube (fitted with a screw cap and a stirring bar). To the crude product (containing a 73:27 mixture of the asymmetric and symmetric dimers, **39b** and **38b**, respectively, which correspond to 1.64 mmol of **39b** and 0.61 mmol of **38b**, considering a quantitative transformation) were then added wet SiO_2 60%$_{w/w}$ (0.5 g/mmol of **39b**, 0.825 g), $NaNO_3$ (2 equiv, 3.29 mmol, 0.280 g), silica/sulfuric acid (2 equiv, 3.29 mmol, 0.902 g),[56] and DCM (9 mL). The mixture was stirred at 45 °C for 40 h, afterward it was diluted with Et_2O (15 mL) and filtered. The solid was washed three more times with Et_2O (3×10 mL), then the combined organic layers were concentrated under vacuum. The recovered crude product was diluted with THF/MeOH 1:2 (12 mL) and treated with a solution of KOH (10.5 mmol, 600 mg) in H_2O. The reaction mixture was refluxed for 2 h, afterward the solvent was evaporated, and the residue acidified with HCl_{aq} 10% (7 mL) and extracted with DCM (2×20 mL). The crude anhydride, obtained after the usual work-up, was purified by flash chromatography on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80). The maleic anhydride **52** was isolated as a yellow oil (0.47 g, 52%); spectroscopic data are in agreement with those reported in literature.[54]

*4.5.2. Preparation of 3-ethyl-4-isopropylfuran-2,5-dione (**66**).* Following the procedure used for the preparation of **52**, 3-(2,2-dichloro-3-methylbutanoyl)-2-ethyliden-[1,3]thiazinane (**54**) (2 mmol, 0.564 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude product (derived from the final hydrolysis step) on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the maleic anhydride **66**, as a yellow oil (0.228 g, 74%), spectroscopic data are in agreement with those reported in the literature.[55]

*4.5.3. Preparation of 3-phenyl-4-methylfuran-2,5-dione (**67**).* Following the procedure used for the preparation of **52**, 3-(dichlorophenylacetyl)-2-ethyliden[1,3]thiazinane (**55**) (2 mmol, 0.632 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude product (derived from the final hydrolysis step) on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the maleic anhydride **67**, as a white solid (0.245 g, 65%), spectroscopic data are in agreement with those reported in the literature.[54]

*4.5.4. Preparation of 3-chloro-4-ethylfuran-2,5-dione (**68**).* Following the procedure used for the preparation of **52**, 3-(dichlorophenylacetyl)-2-ethyliden[1,3]thiazinane (**56**) (2 mmol, 0.549 g), with a catalyst load of 10 mol %, gave, after chromatography of the crude product (derived from the final hydrolysis step) on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the maleic anhydride **68**, as a thick beige oil (0.059 g, 20%), spectroscopic data are in agreement with those reported in the literature.[56]

*4.5.5. Preparation of 3,4-diphenylfuran-2,5-dione (**69**).* Following the procedure used for the preparation of **52**, 3-(dichlorophenylacetyl)-2-(*Z*)-benzyliden[1,3]thiazinane (**57**) (2 mmol, 0.757 g) gave, after chromatography of the crude product (derived from the final hydrolysis step) on silica gel, eluting with a PE/Et_2O gradient (from 100:0 to 20:80), the maleic anhydride **69**, as a white solid (0.375 g, 75%), spectroscopic data are in agreement with those reported in the literature.[57]

Acknowledgements

We thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) for financial support (PRIN 20085E2LXC-004, 20085E2LXC-003).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.117. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14; (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: NY, USA, 1996; Vol. 48, pp 301–586; (c) Ghosez, A.; Giese, B.; Zipse, H. *Houben-Weil*; Georg Thieme: Stuttgart, 1989; Vol. E19a; 1042–1052; (d) Giese, B.; Kopping, B.; Gobel, T.; Kopping, B.; Zipse, H. *Houben-Weil*; Georg Thieme: Stuttgart, 1995; Vol. E21,; 2250–2287.
2. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482–483.
3. For reviews see: (a) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695–713; (b) Parsons, A. F. *C. R. Acad. Sci. Paris—Ser. IIc—Chem.* **2001**, *4*, 391–400.
4. (a) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901–2905; (b) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75–78.
5. For a different opinion see: Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765–10772.
6. Ishibashi, H. *Chem. Rec.* **2006**, *6*, 23–31.
7. (a) Bregoli, M.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Petrillo, G.; Spinelli, D. *Synthesis* **2011**, 1267–1278; (b) Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A. *Tetrahedron* **1999**, *55*, 5839–5852.
8. (a) Galeazzi, R.; Mobbili, G.; Orena, M. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, Italy, 1997; Vol. 1, pp 355–400; (b) Ishibashi, H.; Sato, T.; Ikeda, M. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 85–94; (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4,; Chapter 4.2, pp 779–831.
9. (a) Clark, A. *J. Chem. Soc. Rev.* **2002**, *31*, 1–11; (b) Nagashima, H.; Itoh, K. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 298–307.
10. (a) Murphy, J. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 298–315; (b) Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, 295–297.
11. (a) Clark, A. J.; Dell, C. P.; McDonagh, J. P. *C. R. Acad. Sci. Paris—Ser. IIc—Chem.* **2001**, *4*, 575–579; (b) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615–8618; (c) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619–8623. The radical polar crossover has also been proposed for Ni, Mn(III), Bu_3SnH, and Ce(IV) promoted RCs of enamides: (d) Clark, A. J.; Dell, C. P.; McDonagh, J. M.; Geden, J.; Mawdsley, P. *Org. Lett.* **2003**, *5*, 2063–2066; (e) Ishibashi, H.; Matsukida, H.; Toyao, A.; Tamura, O.; Takeda, Y. *Synlett* **2000**, 1497–1499; (f) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1998**, *39*, 4397–4400; (g) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501–503.
12. (a) Friestad, G. K.; Wu, Y. *Org. Lett.* **2009**, *11*, 819–822; (b) Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221–6231.
13. Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
14. Ghelfi, F.; Stevens, C.; Laureyn, I.; Van Meenen, E.; Rogge, T. M.; De Buyck, L.; Nikitin, K. V.; Grandi, R.; Libertini, M. C.; Pagnoni, U. M.; Schenetti, L. *Tetrahedron* **2003**, *59*, 1147–1157.

15. (a) Ghelfi, F.; Pattarozzi, M.; Roncaglia, F.; Giangiordano, V.; Parsons, A. F. *Synth. Commun.* **2010**, *40*, 1040–1051; (b) Roncaglia, F.; Stevens, C. V.; Ghelfi, F.; Van der Steen, M.; Pattarozzi, M.; De Buyck, L. *Tetrahedron* **2009**, *65*, 1481–1487; (c) Ghelfi, F.; Pattarozzi, M.; Roncaglia, F.; Parsons, A. F.; Felluga, F.; Pagnoni, U. M.; Valentin, E.; Mucci, A.; Bellesia, F. *Synthesis* **2008**, 3131–3141; (d) Bellesia, F.; Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parsons, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746–757; (e) De Buyck, L.; Danieli, C.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F. *Tetrahedron* **2005**, *60*, 2871–2877; (f) De Buyck, L.; Cagnoli, R.; Ghelfi, F.; Merighi, G.; Mucci, A.; Pagnoni, U. M.; Parsons, A. F. *Synthesis* **2004**, 1680–1686.
16. (a) Chen, X.; Zheng, Y.; Shen, Y. *Chem. Rev.* **2007**, *107*, 1777–1830. Also important are the anhydrides and the maleimides carrying one or two aryl groups at the positions C(3) and C(4), they are present in natural products: (b) Aqueveque, P.; Anke, T.; Sterner, O. *Z. Naturforsch.* **2002**, *57c*, 257–262; (c) Rudi, A.; Evan, T.; Aknin, M.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 832–833; (d) Rudi, A.; Goldberg, I.; Stein, Z.; Frolow, F.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Org. Chem.* **1994**, *59*, 999–1003 in fluorescent compounds: (e) Franc, G.; Mazères, S.; Turrin, C.-O.; Vendier, L.; Duhayon, C.; Caminade, A.-M.; Majoral, J.-P. *J. Org. Chem.* **2007**, *72*, 8707–8715; (f) Shigemitsu, Y.; Komiya, K.; Mizuyama, N.; Tominaga, Y. *Dyes Pigments* **2007**, *72*, 271–284; (g) Yeh, H.-C.; Chan, L.-H.; Wu, W.-C.; Chen, C.-T. *J. Mater. Chem.* **2004**, *14*, 1293–1298; (h) Yeh, H.-C.; Wu, W.-C.; Chen, C.-T. *Chem. Commun.* **2003**, 404–405; (i) Fields, E. K.; Beherend, S. J. *J. Org. Chem.* **1990**, *55*, 5165–5170 and in enzymatic inhibitors: (l) Dubernet, M.; Caubert, V.; Guillard, J.; Viaud-Massuard, M.-C. *Tetrahedron* **2005**, *61*, 4585–4593; (m) Lee, J. Y.; Yoon, K. J.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4331–4334; (n) Braña, M. F.; Domínguez, G.; Sáez, B.; Romerdahl, C.; Robinson, S.; Barlozzari, T. *Eur. J. Med. Chem.* **2002**, *37*, 541–551; (o) Braña, M. F.; Fernández, A.; Garrido, M.; Rodríguez, M. L. L.; Morcillo, M. J.; Sanz, A. M. *Chem. Pharm. Bull.* **1989**, *37*, 2710–2712; (p) Sánchez, C.; Méndez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007–1045 substituted maleic anhydrides or maleimides are also synthetically useful, being transformable into other interesting compounds: (q) Babu, K. S.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. *J. Med. Chem.* **2006**, *49*, 7877–7886; (r) Brown, G. D.; Wong, H.-F. *Tetrahedron* **2004**, *60*, 5439–5451; (s) Babidge, P. J.; Massy-Westropp, R. A. *Aust. J. Chem.* **1981**, *34*, 1745–1756.
17. Pattarozzi, M.; Ghelfi, F.; Roncaglia, F.; Pagnoni, U. M.; Parsons, A. F. *Synlett* **2009**, 2172–2175.
18. McElvain, S. M. *Chem. Rev.* **1949**, *45*, 453–492.
19. (a) Beard, D. J.; Pace, C. R.; Pittman, C. U., Jr.; Saebø, S. *Struct. Chem.* **2009**, *20*, 961–967; (b) Ye, G.; Henry, W. P.; Chen, C.; Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2009**, *50*, 2135–2139; (c) Ye, G.; Zhou, A.; Henry, W. P.; Song, Y.; Chatterjee, S.; Beard, D. J.; Pittman, C. U., Jr. *J. Org. Chem.* **2008**, *73*, 5170–5172; (d) Zhou, A.; Pittman, C. U., Jr. *J. Comb. Chem.* **2006**, 262–267; (e) Zhou, A.; Cao, L.; Li, H.; Liu, Z.; Cho, H.; Henry, W. P.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4188–4200; (f) Zhou, A.; Pittman, C. U., Jr. *Synthesis* **2006**, 37–48; (g) Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2005**, *46*, 3801–3805; (h) Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2005**, *46*, 2045–2048; (i) Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2004**, *45*, 8899–8903; (l) Wu, Z.; Stanley, R. R.; Pittman, C. U., Jr. *J. Org. Chem.* **1999**, *64*, 8386–8395; (m) Zhu, P. C.; Lin, J.; Pittman, C. U., Jr. *J. Org. Chem.* **1995**, *60*, 5729–5731.
20. (a) Zhou, A.; Njogu, M. N.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4093–4102; (b) Leśniak, S.; Flisińska, J. *Synthesis* **2001**, 135–139; (c) Naito, T.; Miyata, O.; Kida, N.; Namoto, K.; Ninomiya, I. *Chem. Pharm. Bull.* **1990**, *38*, 2419–2423; (d) Naito, T.; Miyata, O.; Ninomiya, I. *Heterocycles* **1988**, *27*, 1321–1324.
21. (a) Casolari, R.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Spinelli, D. *Tetrahedron* **2011**, *67*, 408–416; (b) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, W.; Huang, J.; Braunecker, W. A.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15309–15314; (c) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249–6253.
22. Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, *264*, 1–62.
23. (a) Csomós, P.; Fodor, L.; Bernáth, G.; Sinkkonen, J.; Salminen, J.; Wiinamäki, K.; Pihlaja, K. *Tetrahedron* **2008**, *64*, 1002–1011; (b) Tohda, Y.; Kawashima, T.; Ariga, M.; Akiyama, R.; Shudoh, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2329–2330; (c) Kiefer, H. *Synthesis* **1972**, 81–82; (d) Durst, T.; du Manoir, J. *Can. J. Chem.* **1970**, *48*, 3749–3752; (e) Marxer, A. *J. Am. Chem. Soc.* **1957**, *79*, 467–472; (f) Sheehan, J. C.; Beck, C. W.; Henery-Logan, K. R.; Ryan, J. J. *J. Am. Chem. Soc.* **1956**, *78*, 4478–4481.
24. Katama, K.; Agata, I. *J. Org. Chem.* **1998**, *63*, 3113–3116.
25. (a) Lee, J.; Lee, K.; Kim, H. *Bull. Korean Chem. Soc.* **1996**, *17*, 115–116; (b) Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287–288.
26. Génisson, Y.; Lauth-de Viguerie, N.; André, C.; Baltas, M.; Gorrinchon, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1017–1023.
27. (a) Li, D.; Zhang, Y.; Zhou, G.; Guo, W. *Synlett* **2008**, 225–228; (b) Jones, R. C. F.; Dimopoulos, P. *Tetrahedron* **2000**, *56*, 2061–2074; (c) Paliakov, E.; Elleboe, T.; Boykin, D. W. *Synthesis* **2007**, 1475–1480.
28. Shabana, R.; Meyer, H. J.; Lawesson, S.-O. *Phosphorus Sulfur* **1985**, *25*, 297–305.
29. (a) Spychala, J. *Monatsh. Chem.* **2006**, *137*, 1203–1210; (b) George, B.; Papadopulos, E. P. *J. Org. Chem.* **1977**, *42*, 441–443.
30. Fuganti, C.; Gatti, F. G.; Serra, S. *Tetrahedron* **2007**, *63*, 4762–4767.
31. (a) Cole, K. P.; Mitchell, D.; Carr, A. M.; Stout, J. R.; Belvo, M. D. *Tetrahedron: Asymmetry* **2009**, *20*, 1262–1266; (b) Fauq, A. H.; Simpson, K.; Maharvi, G. M.; Golde, T.; Das, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6392–6395; (c) Peters, J.-U.; Galley, G.; Jacobsen, H.; Czech, C.; David-Pierson, P.; Kitas, E. A.; Ozmen, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5918–5923.
32. (a) Bagal, S. K.; Adlington, R. M.; Brown, R. A. B.; Baldwin, J. E. *Tetrahedron Lett.* **2005**, *46*, 4633–4637; (b) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100–9108; (c) Bagal, S. K.; Adlington, R. M.; Marquez, R.; Cowley, A. R.; Baldwin, J. E. *Tetrahedron Lett.* **2003**, *44*, 4993–4996.
33. (a) de Sá, A. C. P. F.; Pontes, G. M. A.; dos Anjos, J. A. L.; Santana, S. R.; Bieber, L. W.; Malvestiti, I. *J. Braz. Chem. Soc.* **2003**, *14*, 429–434; (b) Jacobson, R. R.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chim. Acta* **1991**, *181*, 111–118; (c) Tokuda, M.; Satoh, K.; Suginome, H. *Chem. Lett.* **1984**, 1035–1038; (d) Kitagawa, Y.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, *16*, 1859–1862; (e) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988–2995; (f) Nicolaou, K. C.; Papageorgiou, C. D.; Piper, J. L.; Chadha, R. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5846–5851.
34. Ishibashi, H.; Kodama, K.; Kameoka, C.; Kawanami, H.; Ikeda, M. *Tetrahedron* **1996**, *52*, 13867–13880.
35. Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862–4863.
36. Fodor, L.; Szabó, J.; Sohár, P. *Tetrahedron* **1981**, *37*, 963–966.
37. Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334–337.
38. (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021; (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867.
39. So, J.-H.; Boudjouk, P. *Inorg. Chem.* **1990**, *29*, 1592–1593.
40. Bellesia, F.; D'Anna, F.; Felluga, F.; Frenna, V.; Ghelfi, F.; Parsons, A. F.; Spinelli, D. *Synthesis* **2012**, 605–609.
41. (a) Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Ruoho, A. E. *Synthesis* **2006**, 1480–1484; (b) Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509–9511.
42. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343–350.
43. Sheldrick, G. M. *SHELX97, Programs for Crystal Structure Analysis*; University of Göttingen: Göttingen, 1997.
44. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
45. Maguet, M.; Poirier, Y.; Guglielmetti, R. *Bull. Soc. Chim. Fr.* **1978**, *11–12*, 550–560.
46. Papadopulos, E. P.; George, B. *J. Org. Chem.* **1977**, *42*, 2530–2532.
47. Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471–4474.
48. Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857–9862.
49. Skinner, G. S.; Wunz, P. R. *J. Am. Chem. Soc.* **1951**, *73*, 3814–3815.
50. Pathan, M. Y.; Paike, V. V.; Pachmase, P. R.; More, S. P.; Ardhapure, S. S.; Pawar, R. P. *Arkivoc* **2006**, 205–210.
51. Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017–1021.
52. Kodama, Y.; Ori, M.; Nishio, T. *Helv. Chim. Acta* **2005**, *88*, 187–193.
53. (a) McFarland, J. W.; Howes, H. L., Jr.; Conover, L. H.; Lynch, J. E. *J. Med. Chem.* **1970**, *13*, 113–119; (b) Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. J. *Org. Chem.* **2005**, *70*, 334–337.
54. Newman, M. S.; Stalick, W. M. *J. Org. Chem.* **1973**, *38*, 3386–3389.
55. Chikauchi, K.; Ida, M.; Abe, T.; Hiraiwa, Y.; Morinaka, A.; Kudo, T. US 2008/0090825 A1, 2008.
56. Messorosh, A. V.; Trukhin, A. V.; Eliseenkov, E. V. *Tetrahedron* **2008**, *64*, 10849–10852.
57. (a) Periasamy, M. *Organometallics* **2004**, *23*, 6323–6326; (b) Yuan, G.-Q. *Tetrahedron* **2008**, *64*, 5866–5872.
58. Yasumitsu, T. *Synthesis* **1979**, 887–889.
59. Kato, T.; Sakamoto, T. *Yakugaku Zasshi* **1971**, *91*, 1174–1177.