Chemodivergent Conversion of Ketenimines Bearing Cyclic Dithioacetalic Units into Isoquinoline-1-thiones or Quinolin-4-ones as a Function of the Acetalic Ring-Size

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Abstract

C-Alkoxycarbonyl-*C*-phenyl-*N*-aryl ketenimines bearing 1,3-dithiolan-2-yl or 1,3-dithian-2-yl substituents at *ortho*-position of the *C*-phenyl ring respectively transform into isoquinoline-1-thiones and quinolin-4-ones under thermal treatment in toluene solution. The formation of isoquinolinethiones involves a rare degradation of the 1,3-dithiolane ring whereas, in contrast, the 1,3-dithiane ring remains intact during the reaction course leading to quinolin-4-ones. Computational DFT results support that the kinetically favourable mechanism for the formation of isoquinoline-1-thiones proceeds through a [1,5]-hydride shift/6π-electrocyclization cascade followed by a thiirane extrusion process. Alternative mechanistic paths showing interesting electronic reorganization processes have been also scrutinized but resulted not competitive on energetic grounds.

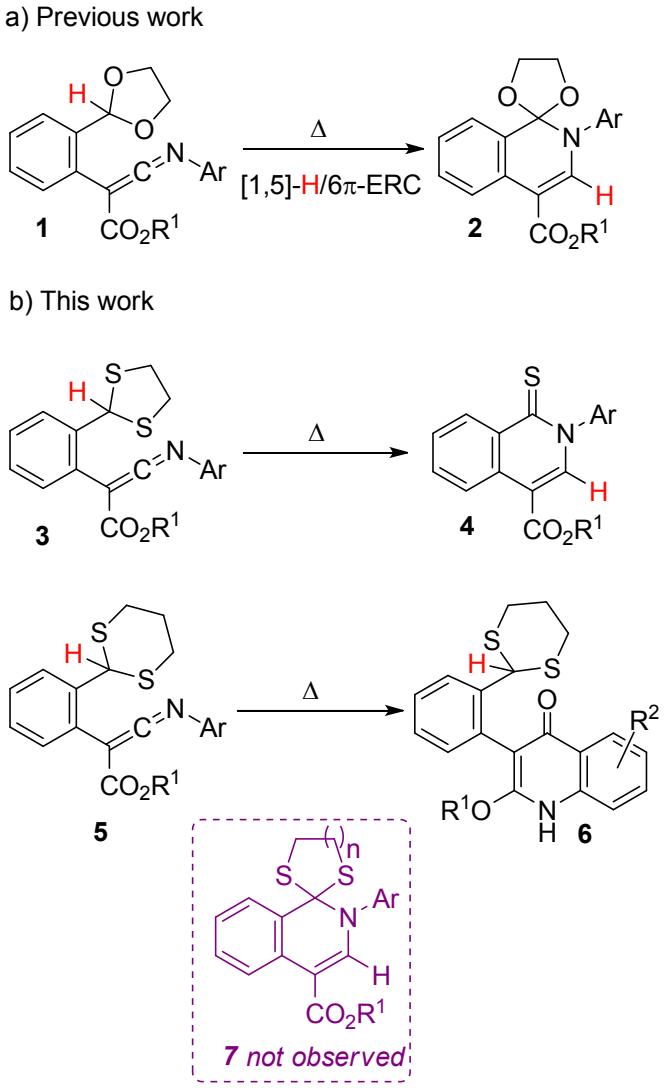
Introduction

Hydrogen atom transfer reactions (HAT) directed towards the functionalization of a C(sp^3)-H bond are of utmost importance in chemical synthesis.[1–4] Among them, intramolecular cyclizations promoted by the migration of a H atom as a *hydride anion* between two sites of a molecular framework have gained considerable attention during the last decades. In such reactions, also known as *internal redox processes*, alkyl groups linked to either ethereal O atoms, tertiary N atoms or aryl rings, and containing C-H bonds, are the typical hydride-donor fragments whereas an electrophilic centre in the same molecule acts as the hydride acceptor, thus yielding transient dipolar structures (intermediates or transition states) that finally cyclizes to the final species.[5–18] Ketenimines are azacumulenic compounds in which the electrophilic central carbon atom is linked by π-bonds to the adjacent carbon and nitrogen atoms. A great number of published works demonstrate the versatile reactivity of ketenimines, for instance, taking part in pericyclic reactions or acting as receptor towards nucleophilic additions.[19–21] In the context of this introduction, our group have contributed to increase the synthetic applications of intramolecular redox cyclizations with seminal works showing the hydride-donor characteristics of acetalic C-H fragments in combination with the hydride-acceptor role played by the central carbon atom of (aza)cumulenes such as ketenimines, carbodiimides, ketenes and allenes in tandem processes delivering spiro- or polycyclic substrates which are difficult to access by other synthetic procedures.[22–28]

In these context we recently reported the synthesis of 1,3-dioxolan-isoquinolines **2** from the *C*-[*ortho*-(1,3-dioxolan-2-yl)phenyl]-*N*-aryl ketenimines **1**.[29] These transformations were proposed to occur through a [1,5]-H/6π-electrocyclic ring closure cascade. In the present work, we initially assumed that the thermal treatment of related ketenimines bearing 1,3-dithiolane (**3**) or 1,3-dithiane functions (**5**) should similarly afford the dithioacetal-isoquinolines **7**. We report herein that, somewhat surprisingly, this is not the case but also that ketenimines **3** and **5** show an interesting chemodivergent reactivity by which the isoquinolinethiones **4** and quinolones **6** are the respective single isolated products in a series of thermally-driven cyclizations in

toluene solution (Scheme 1). Intrigued by the unusual degradation of the 1,3-dithiolane ring during the **3** → **4** conversion we have also studied the mechanism governing the formation of isoquinolinethiones **4** by theoretical methods at DFT levels.

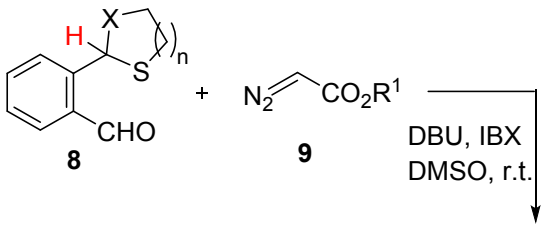
Scheme 1. Thermal treatment of 1,3-dioxolan-ketenimines **1** and 1,3-dithioacetal-ketenimines **3** and **5**.



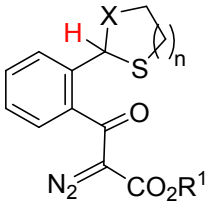
Results and Discussion

Since Staudinger published the first synthesis of ketenimines[30] different methods have been reported for accessing to this kind of azacumulenes.[31,32] Among them, the combination of ketenes and iminophosphoranes has been shown to be a competent protocol.[33] Nevertheless, the high reactivity exhibited by ketenes turns complicated their isolation and further manipulation. In this sense, the decided to synthesize the ketenimines **3** and **5** by reacting different iminophosphonares with *in-situ* generated ketene precursors. Thus, we started with the preparation of diazoacetoacetates **10** which convert into ketenes under thermal conditions through a Wolff rearrangement.[34] Benzaldehydes bearing a (di)thioacetal unit at *ortho*-position **8** were reacted with α-diazoesters **9** in dimethylsulfoxide solution at room temperature and in the presence of a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and the oxidant 2-iodoxybenzoic acid (IBX).[35] After 10-15 h of stirring, diazoacetoacetates **10** were isolated in 50-76% yield (Scheme 2). With diazoacetoacetates **10** in our hands and motivated by the results obtained in our previous work[29] we first explored the ability of the potential dithiolane-ketenes to experiment a tandem [1,5]-H shift/6π-ERC reaction. However, a complex mixture of unidentified products was obtained when toluene solutions of **10a,b** were refluxed.

Scheme 2. Preparation of diazoacetoacetates **10**.



10a, X = S, n = 1, R^1 = Et, 60%
10b, X = S, n = 1, R^1 = Me, 50%
10c, X = O, n = 1, R^1 = Et, 76%
10d, X = S, n = 2, R^1 = Et, 50%



Following our initial strategy, toluene solutions containing diazoacetoacetates **10a-c** and a stoichiometric amount of *N*-aryliminophosphoranes **11** were heated at reflux temperature for 10-15 h. Transient ketenimine intermediates **3** were observed by infrared spectroscopy during the reaction (~2000 cm^{-1}). In contrast to the expected formation of the spiro compounds **7** (n = 1)**,** which would result from a cascade [1,5]-H/6π-ERC sequence, isoquinolinethiones **4a-d** were the single isolated products (Scheme 3) and were fully characterized by ^{1}H and ^{13}C-NMR spectroscopy (see Table 1 and SI). Thus, ^{1}H-NMR spectra of **4a-d** present a singlet at 8.27-8.33 ppm associated with the hydrogen at C3 atom. Their ^{13}C-NMR spectra show a peak at ~188 ppm that matches with the presence of a thiocarbonyl group of the thiolactam function. Taking into account the atomic connectivity of the products **4a-d** it seems that the acetalic hydrogen atom has migrated towards the central carbon atom of the ketenimine motif followed by a ring closure process. Remarkably, the formation of isoquinoline-1-thiones **4** involves the degradation of the 1,3-dithiolane ring, which presumably might be a consequence of the extrusion of either a thiirane molecule or both ethylene and sulphur molecules. A related transformation took place when similar 1,3-oxathiolane-ketenimine **12** (X = O) was subjected to thermal treatment, leading to the isoquinolin-1-one **13**, whereas the formation of the corresponding spiroisoquinoline (**14**) did not occur (Scheme 3).

Scheme 3. Preparation of isoquinoline-1-thiones **4** and isoquinolin-1-one **13**

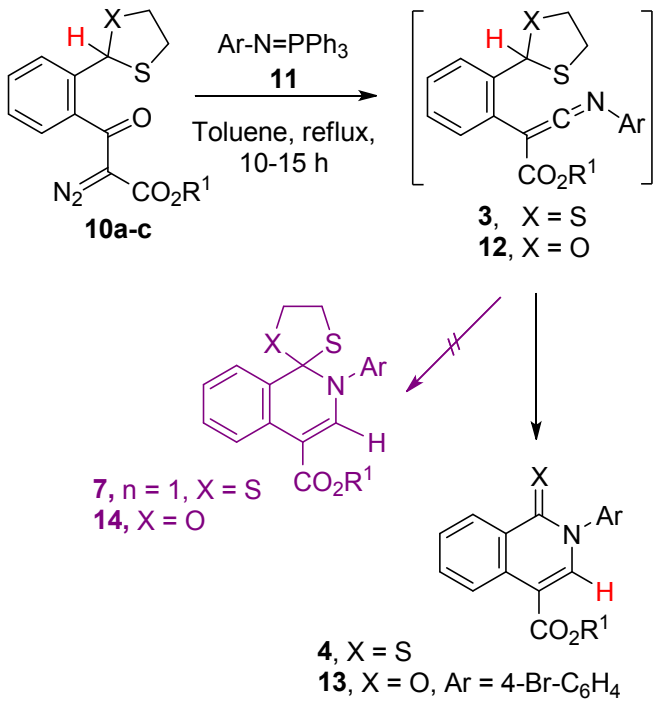
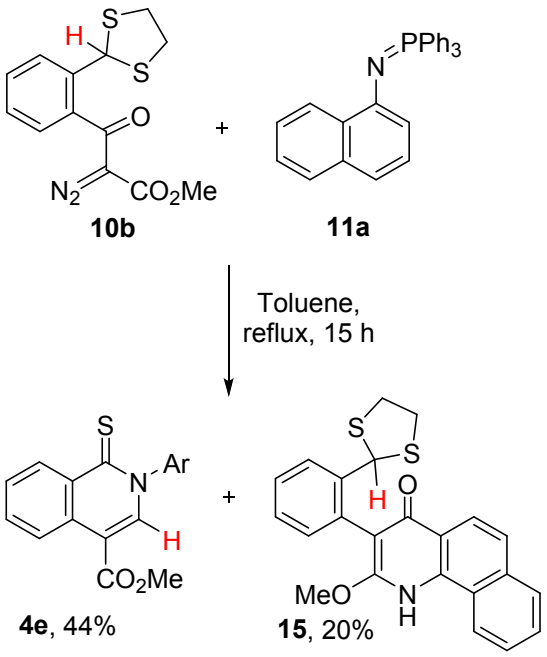


Table 1. Isoquinoline-1-thiones **4** and isoquinol-1-one **13**

Compound	X	Ar	R^1	Yield (%)
4a	S	4-Me-C_6H_4	Et	74
4b	S	4-Me-C_6H_4	Me	70
4c	S	4-MeO-C_6H_4	Et	58
4d	S	1-Naphthyl	Et	60
13	O	4-Br-C_6H_4	Et	50

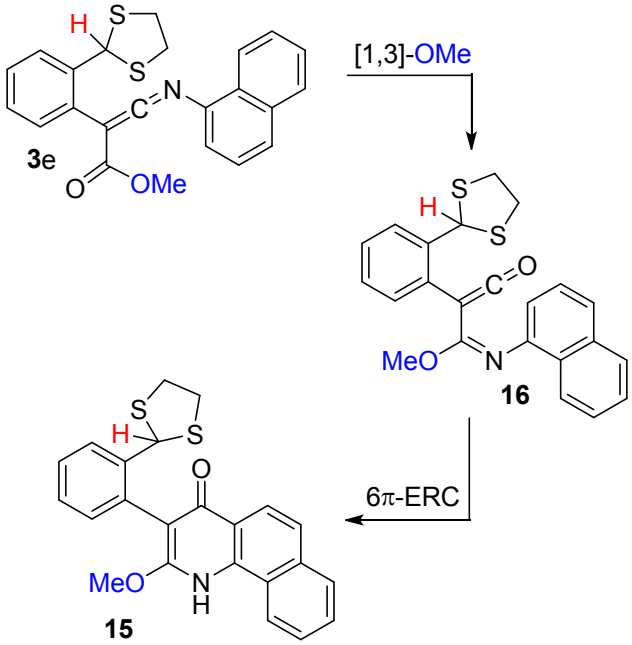
Interestingly, the thermal treatment of the diazoacetoacetate **10b** in presence of *N*-(1-naphthyl) iminophosphorane **11a** delivered the isoquinolinethione **4e** together with the quinolone **15** in 44% and 20% yield, respectively (Scheme 4). Both ^{1}H- and ^{13}C-NMR spectra of **15** reveal that the 1,3-dithiolane group remained unaltered during the course of the reaction whereas the methoxy group migrated to the central carbon atom of the intermediate ketenimine **3e** (n=1, R^1 = Me, Ar= 1-naphthyl).

Scheme 4. Preparation of the isoquinolinethione **4e** and the quinolone **15**



As in previous examples, the transient dithiolane-ketenimine **3e** was identified by infrared spectroscopy during the reaction and the formation of the quinolone **15** could be justified by attending to the results obtained in the thermal treatment of structurally analogous *C*-alkoxycarbonyl-*N*-aryl ketenimines, as reported by Motoyoshiya[36] and Wentrup.[37] Scheme 5 shows the proposed mechanism for the conversions **3e** → **15.** This should proceed by an initial [1,3]-OMe shift from the ester function to the central carbon atom of the ketenimine unit to give the imidoylketene **16** that should then undergo a 6π-ERC to yield the final quinolone **15**. This final step would involve the C=C double bond of the ketene, its conjugated C=N bond and one C=C double bond of the naphthyl group at the N atom.

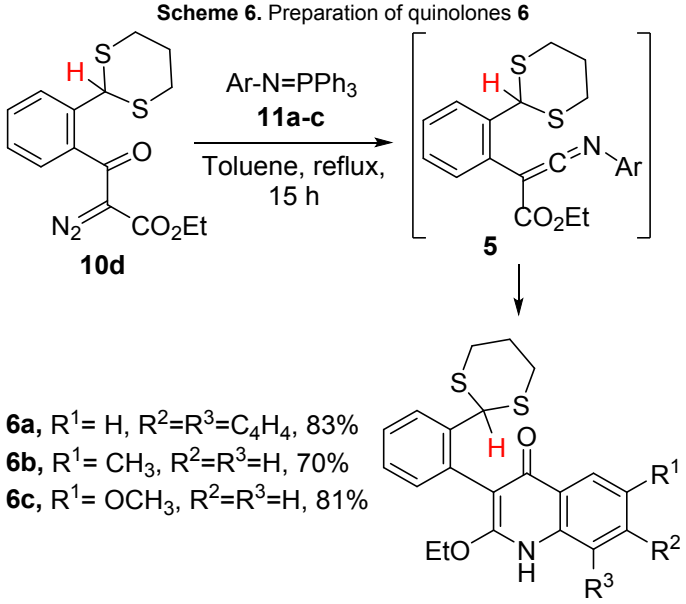
Scheme 5. Mechanistic proposal for quinolone **15**



This later example indicates that both initial hydride and methoxy migration processes could be competitive depending on the reactant. This fact led us to argue that the dual reactivity mode of the transient ketenimines might be modulated. We reasoned that the hydride migration ability would decrease in compounds bearing dithiane units instead of dithiolane,[25] and therefore, the alkoxy migration would be promoted. Added to this, in case of [1,5]-H migration process, the expansion of the dithioacetal ring would probably avoid the degradation of the dithioacetal unit and would perhaps allow the isolation of some of the putative

intermediates as those analogous to spiroisoquinolines **7**. With this strategy in mind, dithiane-diazo compounds **10d** were reacted with iminophosphoranes **11a-c** in toluene solution at reflux temperature for 15 h. This thermal treatment selectively furnished the quinolones **6** in good yields whereas no products from an initial [1,5]-H migration were detected (Scheme 6). The mechanism behind the transformation of ketenimines **5** into quinolones **6** would be similar to that previously commented for the formation of the structurally related quinolone **15** (see Scheme 5).

Scheme 6. Preparation of quinolones **6**

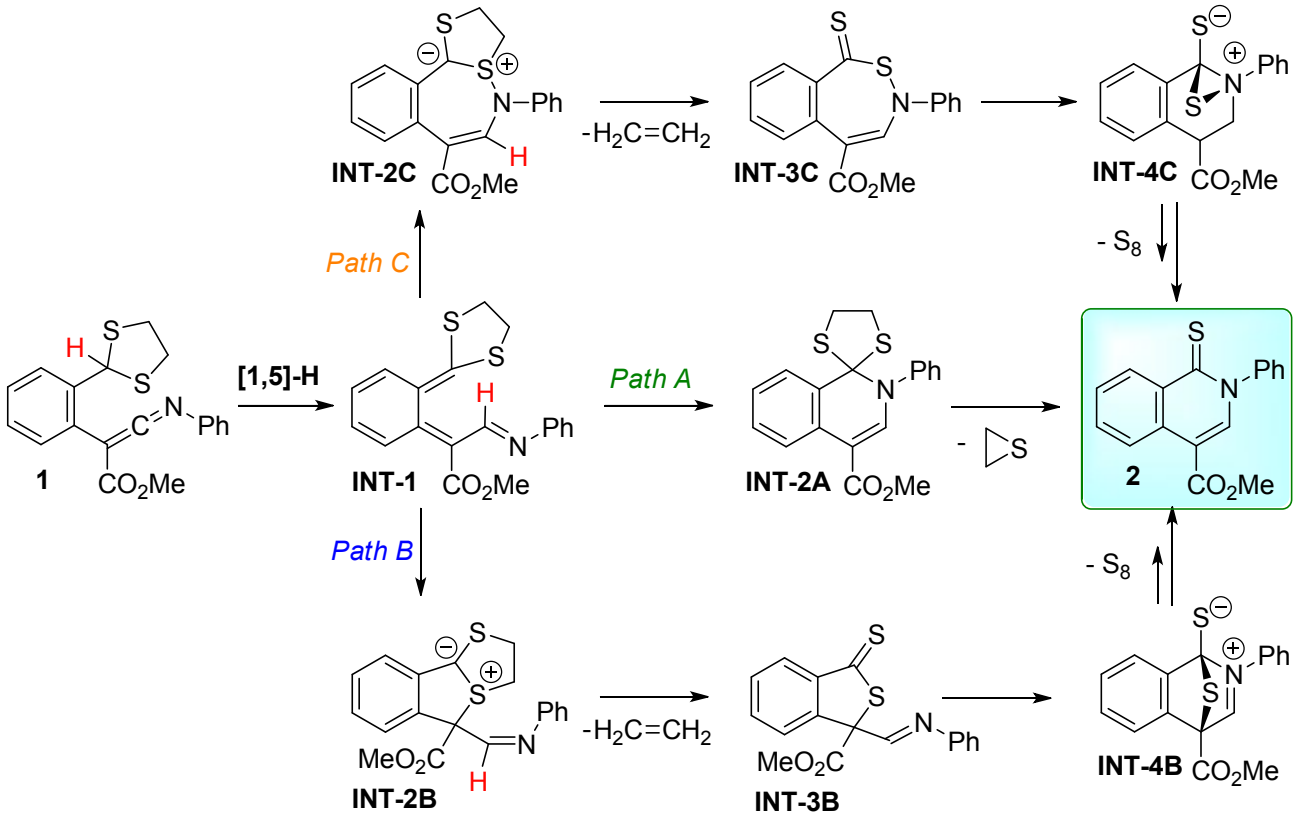


Whereas the lesser propensity of the dithioacetalic H atoms for participating in this type of [1,5]-hydride shifts, in comparison with their acetalic counterparts,[24,25] and the involvement of alkoxy groups from ester functions in 1,3-alkoxy migrations toward the central carbon atom of heterocumulene functions,[36,37] accounting for the resulting quinolones **6** and **15**, have been disclosed in advance and computationally studied, the apparent extrusion of a C_2H_4S fragment (or combination of fragments) in the conversion of ketenimines **3** into isoquinoline-1-thiones **4** merits to be addressed with the aid of a DFT study. We studied this latter transformation at the PCM(toluene)-wB97XD/def2TZVP//PCM(toluene)-B3LYP/6-31+G* theoretical level by exploring the potential energy surface (PES) associated to the conversion of *C*-[*ortho*-(1,3-dithiolan-2-yl)phenyl], *C*-methoxycarbonyl, *N*-phenyl ketenimine (**3f**) into *N*-phenyl-4-methoxycarbonyl-isoquinolin-2-thione (**4f**) (for full details see Supp Info). The qualitative reaction profiles found for this transformation are depicted in Figure 1, while Table 2 discloses the energy barriers computed for each mechanistic step

We have found several paths potentially accounting for these transformations. Some of they finally lead to **4f**, whereas others result in species that can be converted into **4f** by apparently simple and easy sulphur extrusions. Fortunately, in spite of the existence of alternative reaction paths that complicated the analysis of the PES under study, this computational study predicts that one of them is clearly favoured over the rest.

All the located paths start from the intermediate **INT-1** formed in the first step, in which ketenimine **3f** undergoes a [1,5]-H shift leading to **INT-1** via **TS1**, 32.9 kcal·mol^{-1} above in energy than **3f**. Former studies of our group demonstrated that this kind of processes is assisted by the sulphur atoms of the 1,3-dithiolane ring.[7,24,25,27] Then, this intermediate can follow several alternative routes. On the basis of its structure, the mechanistic paths shown in Scheme 7 can be tentatively anticipated. Note that **INT-1** possesses a 1-aza-hexatriene system allowing the formation of a pyridine ring annulated to the *ortho*-phenylene one via a 6π-electrocyclic ring closure giving **INT-2A**. A subsequent retro-[3+2]-cycloaddition with thiirane extrusion would lead to the final product via path A. Moreover, an alternative path B can be conceived involving the 1-thia-butadiene fragment of **INT-1** enabling a different kind of ring closure, a 1,5-cyclization leading to the dipolar intermediate **INT-2B**, which could later lose ethylene giving **INT-3B**. The nucleophilic addition of its iminic nitrogen atom into the thiocarbonylic carbon could lead to the dipolar intermediate **INT-4B** that would evolve to **4f** by sulphur extrusion. And finally, a third route for the evolution of **INT-1** consisting of a 1,7-ring closure through path C can be considered. This process would lead to the tricyclic benzothiazepine **INT-2C**, which by loss of ethylene could evolve to the benzothiazepin-1-thione **INT-3C**. Its conversion through the formation of a six-membered ring by the nucleophilic addition of the nitrogen atom to the thiocarbonylic carbon would lead to the dipolar intermediate **INT4-C**, which could be converted into the final product by sulphur extrusion (see Scheme 7).

Scheme 7. Tentative mechanistic reaction paths for the transformation of ketenimine **3f** into *N*-phenyl-4-methoxycarbonylisoquinolin-1-thione (**4f**)



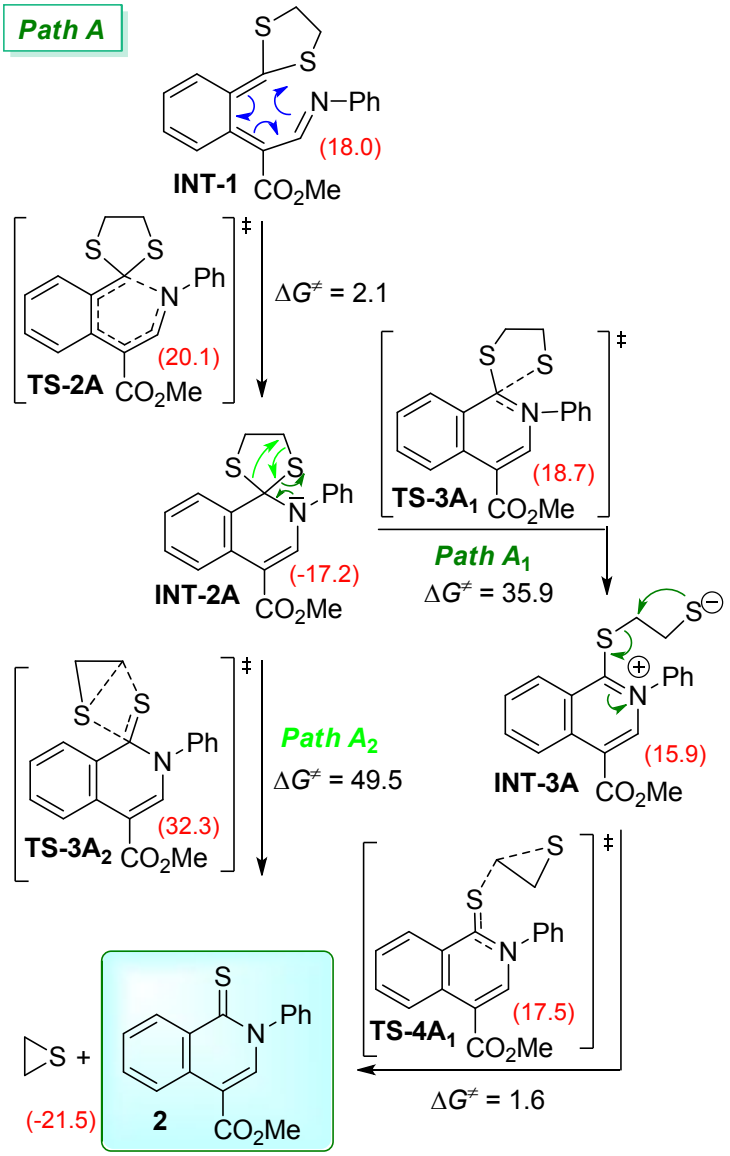
Next, we will discuss in detail each of the mechanistic steps we have found for these three reaction paths.

Following path A, the species **INT-1** is converted into the spiroisoquinoline **INT-2A**. This process takes place via **TS-2A** and shows a very low energy barrier, only 2.1 kcal·mol^{-1} (Scheme 8). This fact can be attributed to the polar nature of this 6π-ERC, with the nitrogen lone pair adding to the electrophilic thioacetalic carbon atom, besides the recovering of aromaticity in going from **INT-1** to **INT-2**. We were able to locate two alternative reaction paths for the evolution of this intermediate (see paths A_1 and A_2 in Figure 1 and Scheme 8). Firstly, we found **TS-3A$_1$** connecting **INT-2A** with the dipolar intermediate **INT-3A**, which via transition structure **TS-4A$_1$** leads to thiirane and the final product **4f**. The computed barrier for the first of these two steps is 35.9 kcal·mol^{-1}, whereas the second one has a very low barrier of 1.6 kcal·mol^{-1}.

It is worth to comment that **TS-3A$_1$** shows some peculiarities. This transition structure accounts for the breaking of one bond between the thioacetalic carbon and one of the sulphur atom, besides the rotation along the C-C bond of the 1,3-dithiolane ring, thus facilitating the thiirane extrusion that will take place in the following step. The distance of the C-S bond being broken is quite large, 4.22 Å (see Figure S2 in the Supporting Info), indicating that in this transition structure this bond is nearly broken. By analysing the motions associated to its imaginary frequency, only the rotation along the C-C bond of the 1,3-dithiolane ring seems to be evident. However, by computing the intrinsic reaction coordinate (IRC), the breaking of that C-S bond can be seen in the earlier steps upwards hill, supporting this transition structure connects **INT-2A** with **INT-3A**. The analysis of the computed NBO charges and bond orders for **INT-2A**, **TS-3A$_1$** and **INT-3A** supports that participation of the nitrogen atom plays a decisive role weakening one of the two thioacetalic carbon-sulphur bonds (see Table S2 in the Supporting Info), thus facilitating the transformation of the 1,3-dithiolane ring into a thiocarbonylic group by extrusion of thiirane.

In the following step, through **TS-4A$_1$**, the negatively charged sulphur atom of **INT-3A** causes a nucleophilic substitution at the methylene linked to the other sulphur atom, that one which is going to form the thiocarbonylic group in **4f**, leading to thiirane and the isoquinolin-1-thione **4f**. This process is predicted to occur easily from **INT-3A**, probably due to the good nucleophilic and leaving group nature of both partners in the SNi reaction, thus explaining that not significant energy barrier has been computed for this step.

Scheme 8. Stationary points found for the conversion of **INT-1** into **4f** at the PCM-B3LYP/6-31+G* theoretical level via paths A_1 and A_2. Energy barriers and relative energies in kcal·mol^{-1} computed at the PCM(toluene)-wB97XD/def2TZVP//PCM(toluene)-B3LYP/6-31+G* theoretical level



The above transformation, **INT-2A** → **4f**, could also take place in one step but the energetic cost would be higher. Thus, we located **TS-3A$_2$**, whose electronic reorganization corresponds to a retro-[3+2]-cycloaddition process leading to thiirane and **4f**. The computed energy barrier is 49.5 kcal·mol^{-1}, 13.6 kcal·mol^{-1} higher than the alternative two-step transformation **INT-2A** → **INT-3A**→ **4f**. The NBO charges and bond orders computed for **TS-3A$_2$** show again the beneficial effect of the lone pair at the nitrogen atom in the breaking of the bond between the thioacetalic carbon and one sulphur atoms (see Support Info).

Similar thiirane extrusions from 1,3-dithiolane-spirocompounds have been previously described by Ueno,[38] Barluenga[39] and Fishwick.[40] Probably, also in these cases the presence of a nitrogen atom linked to the acetalic carbon atom in the molecule that undergoes the thiirane extrusion facilitates the process, although this fact was not explicitly argued.

We also investigated the possibility that triphenylphosphane oxide, formed in the reaction mixture when ketenimine **3f** is generated from the appropriate ketene and iminophosphorane, could catalyse the extrusion of thiirane from **INT-2A**. However, the energy barriers associated to this reaction path are very high compared to those of alternative paths A$_1$ and A$_2$. For clarity, we have excluded this route from the general discussion, but it can be found in the Supporting Info.

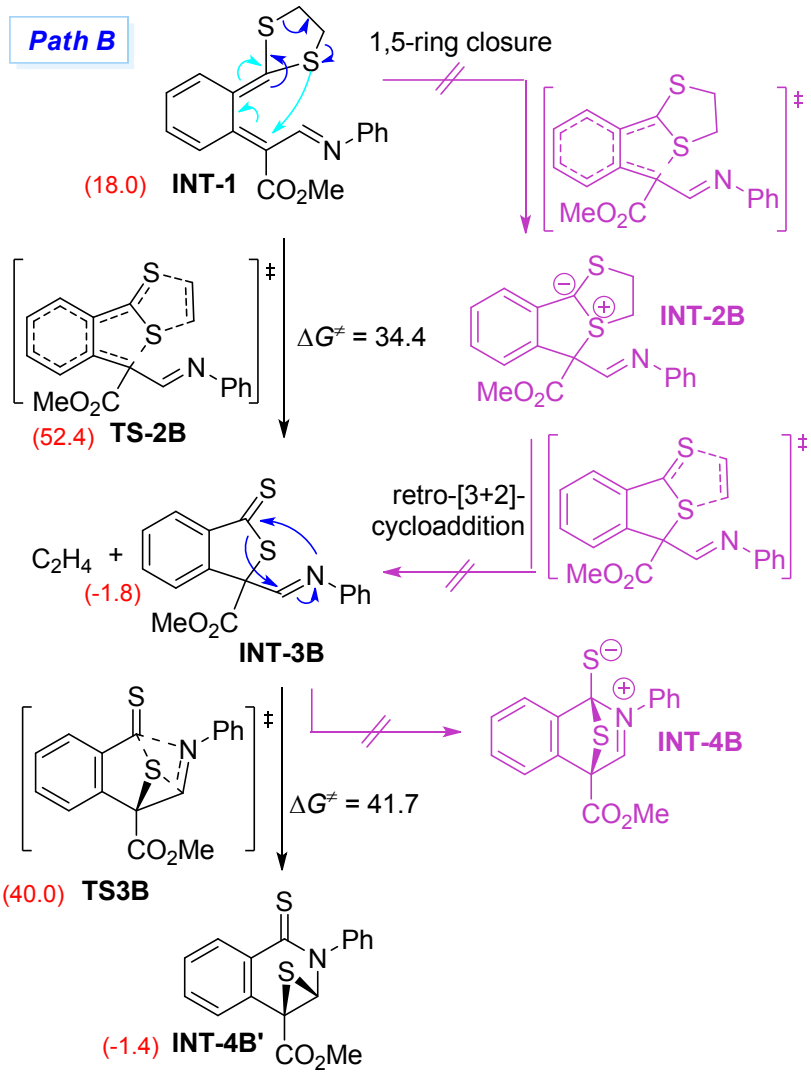
By comparing the heights of the energy barriers corresponding to paths A$_1$ and A$_2$, the predicted reaction path among these three possibilities is neatly path A$_1$.

From **INT-1**, another path that can be reasonably envisaged for the conversion under study entails a 1,5-ring closure, with formation of a new S-C bond, leading to the tricyclic species **INT-2B**. This ylide could evolve via a retro-[3+2]-cycloaddition to give ethylene and the benzo[*c*]thiophene-1-thione (**INT-3B**), as shown in Scheme 9. Contrarily to that expected, we have located **TS-2B**, which directly connect **INT-1** with **INT-3B**. Namely, both processes, the 1,5-ring closure and the retro-[3+2]-cycloaddition, seem to take place simultaneously in a single reaction step. The computed energy barrier is 34.4 kcal·mol^{-1}. Then, species **INT-**

3B provides the dihydrothiireno[2,3-*c*]isoquinoline-3(2*H*)-thione (**INT-4B'**) by addition of the nitrogen atom to the thiocarbonylic carbon atom with simultaneous migration of a sigma bond from that carbon atom to the iminic one, thus generating the thiirane ring shown by **INT-4B'** (instead of leading the species **INT-4B** that initially we had proposed in Scheme 7). The energy barrier computed for this latter step, 41.7 kcal·mol^{-1}, is somewhat higher than the previous one.

The conversion of **INT-1** into **INT-3B** merits some comments. There is an electronic reorganization similar to a 1,5-ring closure with simultaneous retro-[3+2]-cycloaddition. The 1,5-ring closure can be seen as thia-analogous to a 1,5-electrocyclization[41–44] of a pentadienyl anion if the isoelectronic exchange of the carbanionic methylene by the sulphur atom is considered.[45] The simultaneity of these two pericyclic events is quite curious and fascinating. As actually it takes place in a single process, it can be conceived as a vinylogous-thia-retro-ene[23,46] reaction where, instead of a hydrogen atom, it is the sulphur atom that migrates breaking its S-CH_2 bond and making a new S-C bond at the end of the 1-thia-butadiene core. This means that ethylene and the 1-thiabutadiene fragment of **INT-3B** would be the enophile and vinylogous ene components respectively, with sulphur being the migrating atom. This rare conversion has precedent in earlier work from our group,[23] since we found that *N*-[2-(1,3-oxathiolan-2-yl)]phenyl ketenimines, under thermal treatment, are converted into the corresponding benzisothiazol-3-ones via intermediates *ortho*-azaxylylene which experiences similar vinylogous-thia-retro-ene process.[47]

Scheme 9. Stationary points found for the conversion of **INT-1** into **INT-4B'** (path B) at the PCM-B3LYP/6-31+G* theoretical level along with those initially proposed (see main text). Energy barriers and relative energies in kcal·mol^{-1} computed at the PCM(toluene)-wB97XD/def2TZVP//PCM(toluene)-B3LYP/6-31+G* theoretical level



Once intermediate **INT-4B'** is formed, its evolution to the final compound **4f** could be explained by sulphur extrusion. In spite of the number of experimental reactions where species with the thiirane motif evolve by extrusion of sulphur, the mechanistic aspects of this topic have been scarcely treated in the literature. We have not found exhaustive computational studies. Miller

and col.[48] reported on the computationally study of sulphur extrusion from thienothiophene by semiempirical methods, but complete characterization of the overall sulphur extrusion from thiirane intermediates was excluded due its computational cost and complexity. On the basis of the energetic profile of several stationary points, the authors established that the extrusion of atomic sulphur is unfavourable, and proposed thiirane species leading to more stable forms of sulphur. More recently, M. Z. Kassaee et col. have proposed a similar mechanism for explaining the conversion of thiepine into benzene and S_8, where the sulphur-sulphur extraction take also place through benzo-thiirane intermediates, but it not was computationally studied.[49]

An in-depth study of sulphur extrusion from species such as **INT-4B'**, that could lead to the desired **4f** and S_2 or more stable allotropic forms of sulphur, is out of the scope of this work. For this reason, we have only explored the sulphur-sulphur extraction between two molecules of **INT-4B'** leading to **4f** and S_2. This could allow to check if this kind of sulphur extrusion show amenable energy barriers. Our results show that this is the case (see the Supporting Info).

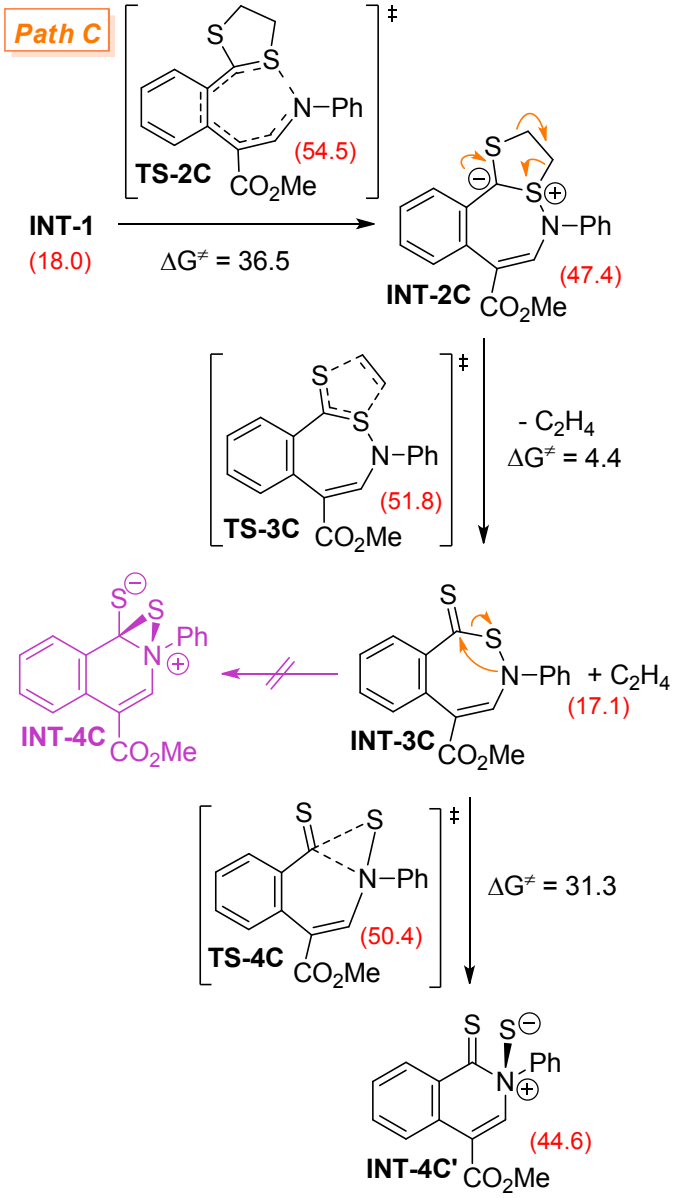
Table 2. Free Gibbs energy barriers[a] computed at the PCM-wB97XD/def2TZVP//PCM-B3LYP/6-31+G* theoretical level for the transformation of ketenimine **3f** into *N*-phenyl-4-methoxycarbonylisoquinolin-2-thione (**4f**), considering toluene as solvent.

Mechanistic Step	$\Delta G^{\neq}_{i}$	$\Delta G^{\neq}_{i\,-1}$
3f $\xrightarrow{TS-1}$ **INT-1**	32.9	14.8
INT-1 $\xrightarrow{TS-2A}$ **INT-2A**	2.1	37.3
INT-2A $\xrightarrow{TS-3A_1}$ **INT-3A**	35.9	2.7
INT-3A $\xrightarrow{TS-4A_1}$ **4f**	1.6	39.0
INT-2A $\xrightarrow{TS-3A_2}$ **4f**	49.5	53.8
INT-1 $\xrightarrow{TS-2B}$ **INT-3B**	34.4	54.2
INT-3B $\xrightarrow{TS-3B}$ **INT-4B'**	41.7	41.4
INT-1 $\xrightarrow{TS-2C}$ **INT-2C**	36.5	7.1
INT-2C $\xrightarrow{TS-3C}$ **INT-3C**	4.4	34.7
INT-3C $\xrightarrow{TS-4C}$ **INT-4C'**	31.3	5.8
ΔG_{rxn} **4f**	-21.5	
ΔG_{rxn} **INT-4B'**	-1.4	
ΔG_{rxn} **INT-4C'**	44.6	

[a] Energy barriers in kcal·mol^{-1}.

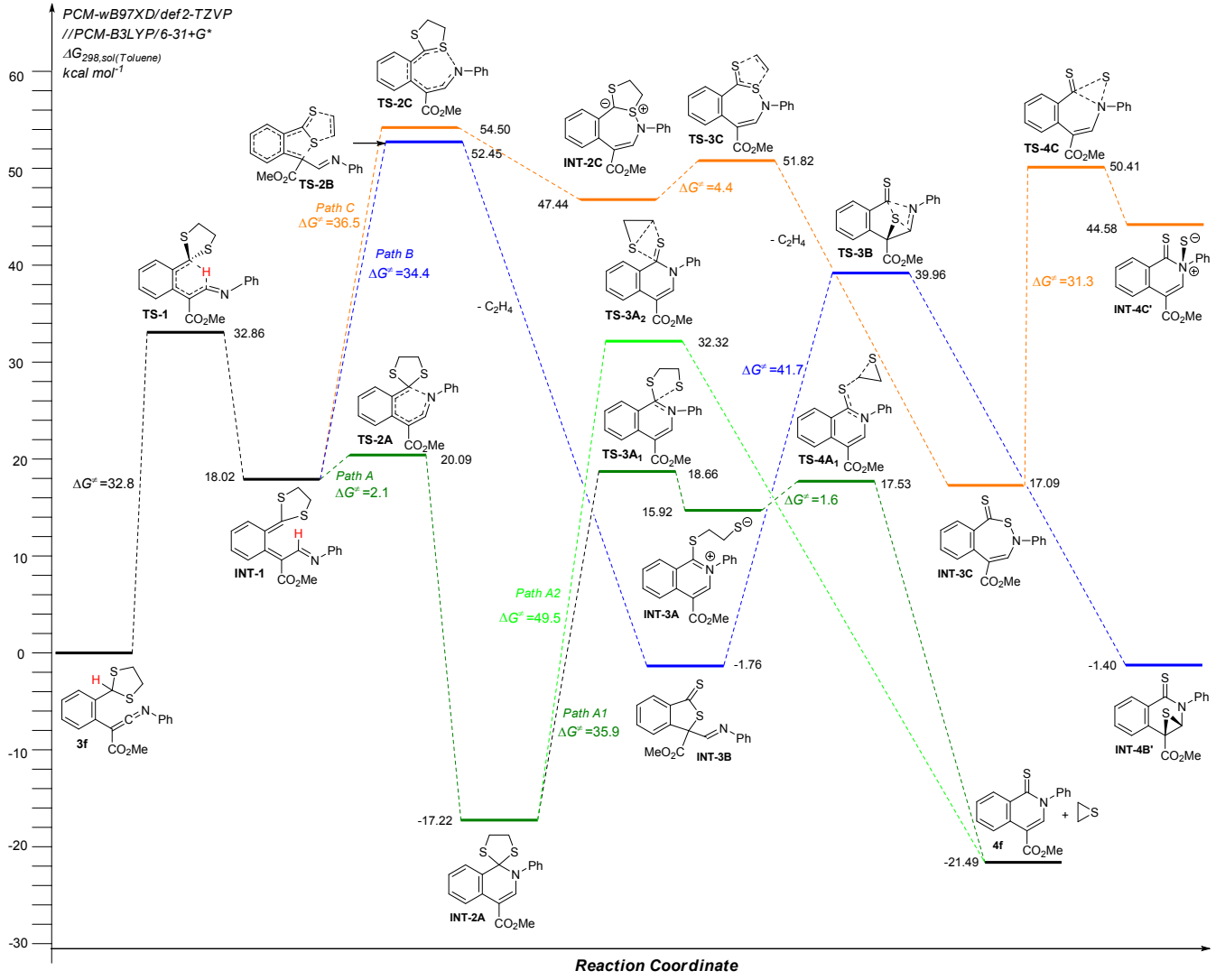
The last mechanistic route we have studied is path C, which can be also seen in the Figure 1 along with the others previously commented, and in Scheme 10. It begins with a 1,7-ring closure via **TS-2C** that provides a S-N bond between the ending atoms of the 1-thia-7-aza-2,4,6-heptatriene system present in **INT-1**, and leads to **INT-2C** with a bridgehead λ^4-sulphur atom. Among the three ring closures of **INT-1** depicted in Figure 1 (i. e. 6π-ERC in path A, 1,5-ring closure/retro-[3+2]-cycloaddition in path B, and 1,7-ring closure in path C), this is the one that shows the highest energy barrier, 36.5 kcal·mol^{-1}. In a subsequent reaction step, **INT-2C** undergoes retro-[3+2]-cycloaddition losing ethylene to give the benzo[*e*][1,2]thiazepine-1(3*H*)-thione **INT-3C** through the transition structure **TS-3C**. The energy barrier for this transformation was computed to be low, 4.4 kcal·mol^{-1}. This can be explained by the favourable formation of the C=S bond shown by **INT-3C**, along with the beneficial ethylene losing.

Scheme 10. Stationary points found at the PCM-B3LYP/6-31+G* level of theory for the conversion of **INT-1** into **INT-4C'** (path C) showing relevant bond distances. Energy barriers and relative energies in kcal·mol^{-1} computed at the PCM(toluene)-wB97XD/def2TZVP//PCM(toluene)-B3LYP/6-31+G* theoretical level



Finally, its evolution by a 6π-electrocyclic ring closure leading to 4-(methoxycarbonyl)-2-phenyl-[1,2]thiazireno[3,2-*a*]isoquinolin-2-ium-8b(2*H*)-thiolate (**INT-4C**) could be easily envisaged (see Scheme 10). However, we located the transition structure **TS-4C** where, simultaneously to the bond making between the thiocarbonylic carbon and the nitrogen atoms, the breaking of the bond joining the thiocarbonylic carbon and the sulphur of the thiazepine ring takes place. Consequently, this process results into the 1-thioxo-1,2-dihydroisoquinolinium 2-thiolate **INT-4C'**, instead of leading to a 1,2-thiaziridine ring annulated to the benzoisoquinoline system as shown in Scheme 10. The energy barrier computed for this conversion is only of 31.3 kcal·mol^{-1}. We assume that **INT-4C'** can be converted to the final **4f** by means of sulphur extrusion processes similar to those commented above.

Figure 1. Qualitative reaction profiles of the mechanistic reaction paths found for the transformation of ketenimine **3f** into *N*-phenyl-4-methoxycarbonyl-isoquinolin-2-thione (**4f**) at the PCM(toluene)-wB97XD/def2TZVP//PCM(toluene)-B3LYP/6-31+G* theoretical level. Energy barriers in kcal·mol^{-1}



By analyzing the reactions profiles depicted in Figure 1, the following points can be inferred:

- The thermal treatment of ketenimine **3f** induces a 1,5-H shift leading to the corresponding *ortho*-xylylene intermediate **INT-1** which can follow three alternative routes, paths A-C, leading to the isoquinolin-1-thione **4f**. Each of them starts with a cyclization involving different heteropolyene fragments of **INT-1**. In this way, path A initiates with a 6π-ERC involving its 1-aza-hexatriene frame. Path B consists of a fascinating vinilogous retro-thia-ene reaction as first step, involving the 1-thiabutadiene fragment of **INT-1**, but also the whole 1,3-dithiolane ring. And path C is the 1-thia-7-aza,2,4,6-heptatriene system of **INT-1** that undergoing a 1,7-ring closure.
- Each path A-C consists in turn of several mechanistic steps and, whereas path A leads directly to the final product **4f**, paths B and C give rise to intermediates which can be converted into **4f** by sulphur extrusion.
- Path A involves the formation of a spiro-1-(1,3-dithiolane-2-yl)isoquinoline in the first step, which can further follow two alternative routes, A_1 and A_2, accounting for thiirane extrusion leading to the isoquinolin-1-thione **4f**. Between them, path A_1 involves the lowest energy cost.
- On the basis of the energy profiles computed for each path, this study predicts that Path A_1 would be the preferred one.

Conclusions

In conclusion, we have reported here the chemodivergent reactivity under thermal conditions of *C*-alkoxycarbonyl-*C*-phenyl-*N*-arylketenimines bearing five- and six-membered dithioacetalic units at *ortho* position of the *C*-phenyl ring. The ketenimines have been prepared *in-situ* by reacting diazoacetoacetates, as ketene precursors, with *N*-aryl iminophosphoranes. Transient 1,3-dithiolane-ketenimines yielded isoquinoline-1-thiones under heating in toluene

whereas in contrast quinolin-4-ones are obtained in the case of ketenimines carrying a larger 1,3-dithiane group. This latter transformation, in which the 1,3-dithiane fragment remains unaltered, has been proposed to occur through a tandem [1,3]-OEt/6π-ERC process. A thorough DFT study has been performed to elucidate the mechanism governing the formation of isoquinolinethiones from 1,3-dithiolane-ketenimines. Our results show that the kinetically favourable path initiates with a [1,5]-hydride shift of the acetalic hydrogen atom towards the central carbon atom of the ketenimine motif followed by a 6π-electrocyclization. Finally, the 1,3-dithiolane ring is degraded by extrusion of a thiirane molecule in a two-step process. Alternative mechanistic paths involving either a vinylogous-thia-retro-ene process or a 1,7-S,N-ring closure have been computationally characterized but are energetically non-competitive.

Experimental Section

General experimental information

All of the melting points are uncorrected. IR spectra were recorded as Nujol mulls or as neat samples. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300 or 400 MHz. $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ at 75 or 100 MHz. The chemical shifts are reported in ppm (δ), relative to the resonance of $CDCl_3$ at δ = 7.26 ppm and of DMSO-d_6 at δ = 2.50 ppm for ^{1}H and for $^{13}C\{^1H\}$ relative to the resonance of $CDCl_3$ δ = 77.16 ppm and of DMSO-d_6 at δ = 39.5 ppm. Mass spectrometry was recorded on HPLC-MS TOF 6220 instrument.

Materials: 2-(2-bromophenyl)-1,3-oxathiolane, *N*-formylpyperidine and ethyl/methyl diazoacetate were commercially available. The following substrates have been prepared according to the literature: 2-(1,3-dithiolan-2-yl)benzaldehyde **8a**,[50] 2-(1,3-oxathiolan-2-yl)benzaldehyde **8c**,[10] 2-(1,3-dithian-2-yl)benzaldehyde **8d**[51] and iminophosphoranes **11**.[52]

General procedure for the preparation of isoquinolinethiones 4, quinolones 6 and 15 and isoquinolonone 13.

To a solution of ethyl diazoacetate (0.18 g, 1.57 mmol) or methyl diazoacetate (0.16 g, 1. mmol) in dimethyl sulfoxide (7 mL) at room temperature were added in succession DBU (0.021 mL, 0.14 mmol), the appropriate aldehyde **8** (1.33 mmol), and a solution of IBX (0.74 g, 2.63 mmol) in dimethyl sulfoxide (7 mL). After 10 h, then the reaction was quenched with aqueous $NaHCO_3$ (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (3 x 60 mL) and with water (100 mL). Finally, they were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate, 4:1 v/v) to afford the corresponding diazoacetoacetates **10**, which were using immediately in the next step.

Typically, a solution containing the appropriate diazoacetoacetate **10** (0.35 mmol) and iminophosphorane **11** (0.35 mmol), in anhydrous toluene (10 mL), was heated at reflux temperature for 10-15 h (6 h in case of **13**). After cooling down, the solvent was removed under reduced pressure and the resulting crude material was purified by column chromatography on silica gel.

Next, a larger scale procedure is shown for the synthesis of **4a**.

4-Ethoxycarbonyl-2-(4-methyl)phenyl-2*H*-isoquinoline-1-thione (4a)

A solution containing the ethyl diazoacetoacetate **10** (0.35 g, 1.1 mmol) and (4-methyl)phenyliminophosphorane (0.40 g) 1.1 mmol), in anhydrous toluene (20 mL), was heated at reflux temperature for 10 h. After cooling down, the solvent was removed under reduced pressure and the resulting crude material was purified by column chromatography on silica gel.

Eluent for chromatography column: hexanes/diethyl ether (4:1, v/v); 0.26 g; yield: 74%; mp: 165-167 ºC; yellow prisms (diethyl ether); IR (Nujol) v: 1713 (vs), 1509 (m), 1483 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 3 H, *J* = 7.2 Hz), 2.44 (s, 3 H), 4.36 (q, 2 H, *J* = 7.2 Hz), 7.24 (d, 2 H, *J* = 8.1 Hz), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.60 (td, 1 H, *J* = 8.4, 1.5 Hz), 7.78 (td, 1 H, *J* = 8.4, 1.5 Hz), 8.27 (s, 1 H), 8.89 (d, 1 H, *J* = 8.4 Hz), 9.10 (d, 1 H, *J* = 8.4 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 14.4 (CH_3), 21.4 (CH_3), 61.3 (CH_2), 111.3 (s), 125.7 (CH), 126.7 (2 x CH), 128.9 (CH), 129.7 (s), 130.5 (2 x CH), 133.0 (CH), 133.5 (CH), 134.4 (s), 139.3 (CH + s), 143.4 (s), 164.9 (s), 188.4 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2S$ 324.1053; Found 324.1055.

4-Methoxycarbonyl-2-(4-methyl)phenyl-2*H*-isoquinoline-1-thione (4b).

Eluent for chromatography column: hexanes/diethyl ether (4:1, v/v); 75 mg; yield: 70%; mp: 170-172 ºC; yellow prisms (diethyl ether); IR (Nujol) v: 1702 (vs), 1508 (m), 1480 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3 H), 3.89 (s, 3 H), 7.24 (d, 2 H, *J* = 7.8 Hz), 7.36 (d, 2 H, *J* = 7.8 Hz), 7.60 (t, 1 H, *J* = 7.2 Hz), 7.80 (t, 1 H, *J* = 7.2 Hz), 8.30 (s, 1 H), 8.90 (d, 1 H, *J* = 8.4 Hz), 9.11 (d, 1 H, *J* = 8.4 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 21.4 (CH_3), 52.2 (CH_3), 100.9 (s), 125.6 (CH), 126.7 (2 x CH), 129.0 (CH), 129.6 (s), 130.5 (2 x CH), 133.0 (CH), 133.6 (CH), 134.4 (s), 139.3 (s), 139.5 (CH), 143.4 (s), 165.3 (s), 188.5 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_2S$ 310.0896; Found 310.0906.

4-Ethoxycarbonyl 2-(4-methoxy)phenyl-2*H*-isoquinoline-1-thione (4c).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 62 mg; yield: 58%; mp: 135-137 ºC; yellow prisms (hexanes); IR (Nujol) v: 1715 (vs), 1615 (s), 1485 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, 3 H, *J* = 7.2 Hz), 3.88 (s, 3 H), 4.39 (q, 2 H, *J* = 7.2 Hz), 7.06 (d, 2 H, *J* = 9.0 Hz), 7.29 (d, 2 H, *J* = 9.0 Hz), 7.60 (td, 1 H, *J* = 8.1, 1.2 Hz), 7.79 (td, 1 H, *J* = 8.1, 1.2 Hz), 8.29 (s, 1 H), 8.90 (dd, 1 H, *J* = 8.6, 0.6 Hz), 9.12 (dd, 1 H, *J* = 8.6, 0.6 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 14.3 (CH_3), 55.5 (CH_3), 61.1 (CH_2), 111.1 (s), 114.8 (2 x CH), 125.5 (CH), 128.0 (2 x CH), 128.8 (CH), 129.6 (s), 132.9 (CH), 133.4 (CH), 134.3 (s), 138.7 (s), 139.4 (CH), 159.6 (s), 164.8 (s), 188.6 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H - S]^+$ Calcd for $C_{19}H_{18}NO_3$ 308.1281; Found 308.1279.

4-Ethoxycarbonyl-2-(1-napthyl)-2*H*-isoquinoline-1-thione (4d).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 75 mg; yield: 60%; mp: 165-167 ºC; yellow prisms (hexanes); IR (Nujol) v: 1715 (vs), 1612 (s), 1481 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3 H, *J* = 7.2 Hz), 4.36 (q, 2 H, *J* = 7.2 Hz), 7.39 (d, 1 H, *J* = 9.0 Hz), 7.46-7.60 (m, 3 H), 7.63-7.69 (m, 2 H), 7.86 (td, 1 H, *J* = 8.4, 1.5 Hz), 8.01 (dd, 2 H, *J* = 13.5, 8.1 Hz), 8.31 (s, 1 H), 8.98 (d, 1 H, *J* = 8.4 Hz), 9.15 (dd, 1 H, *J* = 8.4, 0.9 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 14.3 (CH_3), 61.3 (CH_2), 111.6 (s), 122.4 (CH), 125.1 (CH), 125.7 (CH), 125.8 (CH), 127.0 (CH), 127.7 (CH), 128.6 (s), 128.8 (CH), 129.0 (CH), 129.7 (CH), 129.8 (s), 132.9 (CH), 133.7 (CH), 134.4 (s), 134.5 (s), 139.7 (CH), 142.3 (s), 164.9 (s), 188.4 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}NO_2S$ 360.1053; Found 360.1052.

4-Methoxycarbonyl-2-(1-napthyl)-2*H*-isoquinoline-1-thione (4e).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 53 mg; yield: 44%; mp: 142-144 ºC; yellow prisms (hexanes); IR (Nujol) v: 1715 (vs), 1615 (s), 1481 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3 H), 7.39 (d, 1 H, *J* = 8.4 Hz), 7.48-7.58 (m, 3 H), 7.62-7.69 (m, 2 H), 7.86 (td, 1 H, *J* = 7.2, 1.5 Hz), 8.00 (dd, 2 H, *J* = 13.5, 8.1 Hz), 8.33 (s, 1 H), 9.00 (d, 1 H, *J* = 8.4 Hz), 9.15 (dd, 1 H, *J* = 8.4, 0.9 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 52.2 (CH_3), 111.2 (s), 122.4 (CH), 125.1 (CH), 125.7 (CH), 125.8 (CH), 127.0 (CH), 127.8 (CH), 128.6 (s), 128.8 (CH), 129.1 (CH), 129.8 (s), 129.9 (CH), 132.9 (CH), 133.8 (CH), 134.5 (s), 134.6 (s), 140.0 (CH), 142.3 (s), 165.3 (s), 188.5 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}NO_2S$ 346.0896; Found 346.0894.

3-(2-(1,3-Dithian-2-yl)phenyl)-2-ethoxybenzo[*h*]quinolin-4(1*H*)-one (6a).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 125 mg; yield: 83%; mp: 156-158 ºC; colourless prisms (hexnes); IR (Nujol) v: 3509 (s), 1619 (vs), 1481 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, 3 H, *J* = 7.2 Hz), 1.84-1.93 (m, 1 H), 2.00-2.05 (m, 1 H), 2.73-2.84 (m, 4 H), 4.62-4.76 (m, 2 H), 5.04 (s, 1 H), 5.83 (s, 1 H), 7.29 (d, 1 H, *J* = 7.2 Hz), 7.45 (td, 1 H, *J* = 7.2, 1.2 Hz), 7.52 (td, 1 H, *J* = 7.2, 1.2 Hz), 7.65-7.73 (m, 3 H), 7.90-7.94 (m, 2 H), 8.11 (d, 1 H, *J* = 9.2 Hz), 9.21 (d, 1 H, *J* = 9.2 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 25.0 (CH_2), 31.7 (CH_2), 32.5 (CH_2), 48.6 (CH), 62.1 (CH_2), 106.4 (s), 113.8 (s), 120.0 (CH), 123.8 (CH), 124.6 (CH), 126.3 (CH), 127.8 (2 x CH), 129.2 (CH), 129.3 (s), 129.4 (CH), 129.9 (CH), 130.6 (s), 131.8 (CH), 134.4 (s), 140.1 (s), 144.8 (s), 158.1 (s), 160.0 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}NO_2S_2$ 434.1243; Found 434.1260.

3-(2-(1,3-Dithian-2-yl)phenyl)-2-ethoxy-6-methylquinolin-4(1*H*)-one (6b).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 101 mg; yield: 70%; mp: 120-123 ºC; colorless prisms (hexanes); IR (Nujol) v: 3333 (s), 1700 (s), 1581 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3 H, *J* = 7.2 Hz), 1.80-1.88 (m, 1 H), 2.00-2.06 (m, 1 H), 2.50 (s, 3 H), 2.70-2.82 (m, 4 H), 4.44-4.52 (m, 2 H), 4.94 (s, 1 H), 6.58 (br s, 1 H), 7.19 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.35-7.50 (m, 3 H), 7.83-7.88 (m, 2 H), 7.95 (s, 1 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 14.5 (CH_3), 21.4 (CH_3), 25.0 (CH_2), 31.8 (CH_2), 32.4 (CH_2), 48.5 (CH), 63.4 (CH_2), 106.1 (s), 118.1 (s), 122.1 (CH), 125.2 (CH), 129.0 (CH), 129.3 (CH), 129.7 (CH), 131.8 (CH), 132.6 (CH), 133.4 (s), 139.8 (s), 143.2 (s), 159.7 (s), 159.8 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}NO_2S_2$ 398.1243; Found 398.1237.

3-(2-(1,3-Dithian-2-yl)phenyl)-2-ethoxy-6-methoxyquinolin-4(1*H*)-one (6c).

Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 117 mg; yield: 81%; mp: 127-129 ºC; colorless prisms (chloroform); IR (Neat) v: 3333 (s), 1700 (s), 1581 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 60 ºC, 300 MHz) δ 1.20 (t, 3 H, *J* = 7.2 Hz), 1.67-1.72 (m, 1 H), 1.90-1.95 (m, 1 H), 2.71-2.78 (m, 3 H), 3.87 (s, 3 H), 4.28-4.38 (m, 2 H), 4.95 (s, 1 H), 7.14 (d, 1 H, *J* = 7.5 Hz), 7.28-7.41 (m, 3 H), 7.61-7.69 (m, 3 H), 7.95 (s, 1 H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 60 ºC, 75 MHz) δ 14.0 (CH_3), 24.4 (CH_2), 30.8 (CH_2), 31.0 (CH_2), 48.0 (CH), 55.2 (CH_3), 61.0 (CH_2), 102.3 (CH), 106.6 (s), 119.2 (s), 120.3 (CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 131.4 (CH), 131.8 (CH), 138.6 (s), 140.4 (s), 154.9 (s), 158.6 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}NO_3S_2$ 414.1192; Found 414.1205.

4-Ethoxycarbonyl-(4-bromo)phenyl-2*H*-isoquinolin-1-one (13)

Eluent for chromatography column: hexanes/diethyl ether (4:1, v/v);65 mg; yield: 50%; mp: 183-185 ºC; yellow prisms (diethyl ether); IR (Nujol) v: 1721 (vs), 1676 (m), 1485 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, 3 H, *J* = 7.6 Hz), 4.38 (q, 2 H, *J* =

7.6 Hz), 7.33-7.36 (m, 2 H), 7.56 (td, 1 H, *J* = 7.8, 1.2 Hz), 7.64-7.67 (m, 2 H), 7.78 (td, 1 H, *J* = 7.8, 1.2 Hz), 8.16 (s, 1 H), 8.47 (dd, 1 H, *J* = 8.0, 1.2 Hz), 8.85 (d, 1 H, *J* = 8.4 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 14.4 (CH_3), 61.0 (CH_2), 107.7 (s), 122.7 (s), 125.5 (CH), 125.6 (CH), 127.7 (CH), 128.5 (CH), 128.6 (2 x CH), 132.7 (2 x CH), 133.6 (CH), 134.3 (s), 139.4 (CH), 139.5 (s), 161.9 (s), 165.1 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}BrNO_3$ 372.0230; found: 372.0239.

3-(2-(1,3-Dithiolan-2-yl)phenyl)-2-methoxybenzo[*h*]quinolin-4(1*H*)-one (15).
Eluent for chromatography column: hexanes/ethyl acetate (4:1, v/v); 29 mg; yield: 20%; yellow oil; IR (Neat) v: 3510 (s), 1619 (s), 1480 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.22-3.29 (m, 2 H), 3.36-3.54 (m, 2 H), 4.16 (s, 3 H), 5.50 (s, 1 H), 7.24 (m, 1 H), 7.42 (td, 1 H, *J* = 7.8, 1.5 Hz), 7.54 (td, 1 H, *J* = 7.8, 1.5 Hz), 7.65-7.74 (m, 3 H), 7.90-7.93 (m, 1 H), 8.05-8.09 (m, 2 H), 9.20-9.22 (m, 1 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 40.1 (CH_2), 40.4 (CH_2), 52.5 (CH), 54.0 (CH_3), 106.3 (s), 113.9 (s), 119.7 (CH), 124.2 (CH), 124.6 (CH), 126.4 (CH), 127.8 (CH), 127.9 (CH), 128.9 (CH), 129.6 (s), 129.8 (CH), 129.9 (CH), 130.5 (s), 130.8 (CH), 134.4 (CH), 142.6 (CH), 144.7 (s), 157.9 (s), 160.0 (s) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_2S_2$ 406.0930; Found 406.0931.

Associate Content

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx
^1H and $^3C\{^1H\}$ NMR spectra, computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

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