"How reaction conditions may influence the regioselectivity in the synthesis of 2,3-dihydro-1,4-benzoxathiine derivatives"

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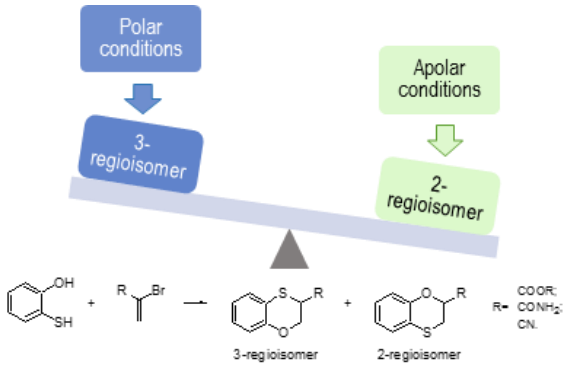


Abstract

The exploration of different reaction conditions aiming to obtain both 2,3-dihydro-1,4-benzoxathiine-2-yl derivatives and 2,3-dihydro-1,4-benzoxathiine-3-yl ones is here reported.

The treatment of 1,2-mercaptophenol with an organic base and a specific 2-bromo acrylate results in a solvent- and substrate- dependent exclusive solvation of O- and S- anions, thus managing the regioselectivity.

Introduction

1,4-benzoxathiane is a common scaffold of a copious number of therapeutic agents, having specific biological activities. The most significant and deeply studied derivatives are the ones showing antihypertensive properties,[1] by blocking α-1 and α -2 adrenoreceptor activity.[2] Others have been considered, due to their sweetness properties,[3] and only recently 2,3-dihydro-1,4-benzoxatins were examined and further evaluated as anticancer agents.[4,5] Specifically, these purine analogs act against the MCF-7 cancer cell line, showing activity towards several protein kinases, as GP132, ERN1 or RAC1, and inducing apoptosis and then cancer cell death.

Even if this scaffold is quite ubiquitous and of high pharmacological relevance, the chemistry of the 1,4-benzoxathiane scaffold seems scarcely exploited. To the best of our knowledge, the few existing synthetic procedures are dated, with harsh reaction conditions or troublesome work-up, and almost exclusively directed to 2-substituted derivatives (Scheme 1). [6-13]

The first synthetic work[6] for the obtainment of this class of compounds concerns non-substituted 1,4-benzoxathianes (Scheme 1-A); Parham and coworkers used a strong-base catalysis, sodium methoxide, and yielded the desired and unstable products with only poor yields.

This initial synthetic pathway was then fully overcome in the following years by one-pot procedures[7,8] (Scheme 1-B), in which suitably substituted cyclohexanones were treated with 1,2-mercaptoethanol and a bromine source (NBS or $CuBr_2$). Large amounts of bromine equivalents were required, being responsible of thio-acetalization, ring expansion and aromatization. This tandem reaction, even if quite convenient and versatile in several conditions, is limited by the impossibility of usage in case of oxidative- or halogen- sensitive products.

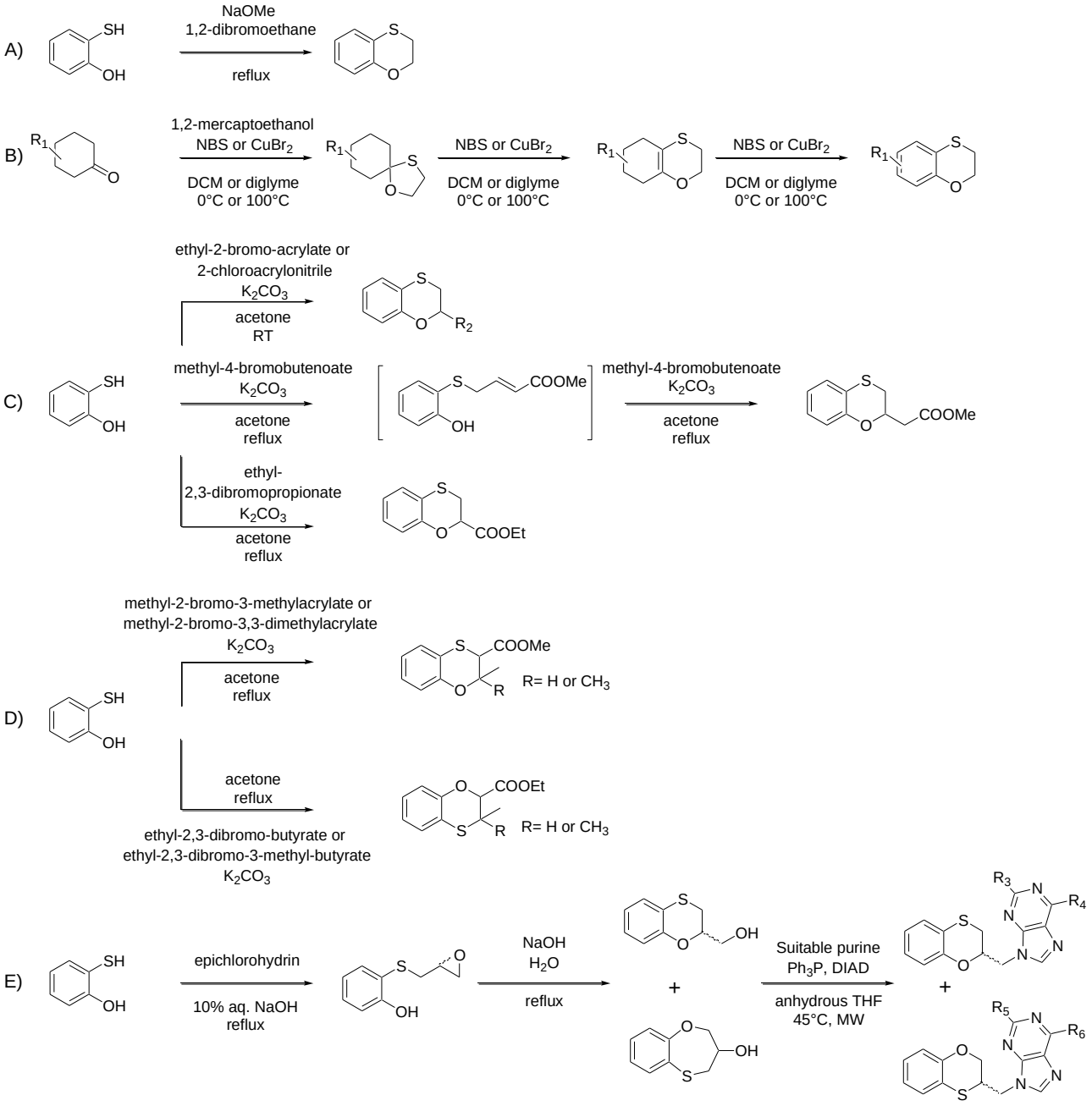
Further additional studies involved the treatment of 1,2-mercaptophenol with α-halo Michael acceptors[9], methyl-4-bromobutenoate[10] or 2,3-dibromopropyl derivatives[11], in acetone and using potassium carbonate as base (Scheme 1-C). In almost the totality of these works, the unique reaction products revealed to be the 2-substituted 1,4-benzoxathianes. Such a result was explained by the greater nucleophilicity of the sulfur as compared with oxygen and by the greater acidity of thiophenol as compared to phenol.[12,13] Sulfur atom is thus responsible for the initial nucleophilic attack on the primary carbon atom of the suitable reactive. The consequent ring closure, achieving the 2-substituted derivatives, proved to be mostly simultaneous, due to the high reactivity of the reaction intermediate.

Literature showed the sole obtainment of 3-substituted 1,4-benzoxathianes only when β-methyl and β,β-dimethyl substituents were present in the α-halo Michael acceptors[9] (Scheme 1-D). Several alternative mechanisms were proposed in order to explain this opposite behavior; nevertheless, no reaction intermediates could be isolated to support those hypotheses. Furthermore, a few years later, Cocco and coworkers[14] achieved 3-methyl or 3,3-dimethyl 2-substituted 1,4-benzoxathianes in a similar manner, thus confusing the interesting result obtained before.

Besides, only in the latest decade, Campos and coworkers[4,5] (Scheme 1-E) reported the obtainment of both 2,3-dihydro-1,4-benzoxathiine-2-yl and 3-yl methylpurines. These derivatives were accomplished through an initial treatment of the 1,2-mercaptophenol with epichlorohydrin and the consecutive Mitsunobu reaction, affording both the substituted derivatives, in different percentages.

In the first step, as already seen by Cabiddu, [15] the reaction of 1,2-mercaptophenol with epichlorohydrins affords both the six-membered and the seven-membered rings, as a consequence of the different nucleophilic attack by the phenoxide ion at the less or the more hindered position of the epoxide. This was explained as a consequence of the larger atomic radius of the sulfur atom versus the oxygen one, which causes primarily the attack at the secondary carbon atom of the epoxide, thus affording the 1,5-benzoxathiepine derivative. Nevertheless, the 2-substituted six-membered ring was anyway accomplished, even if only in 20-30 % yields. The second step, that is the microwave-assisted Mitsunobu coupling, brought, on one side, to the final 2,3-dihydro-1,4-benzoxathiin-2yl-methylpurine and, on the other, to the contraction of the 1,5-benzoxathiepine into the six-membered 3- substituted 2,3-dihydro-1,4-benzoxathiine.

SCHEME 1*: Literature background*

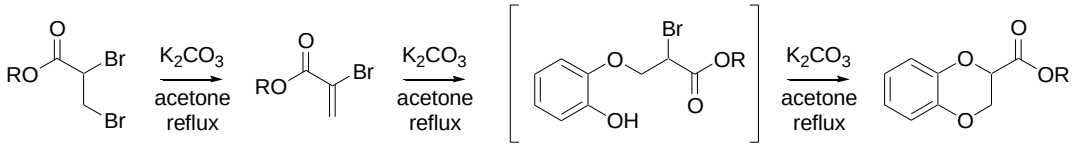


While working on the synthesis of innovative antibacterial agents,[16,17] acting as FtsZ inhibitors, we designed 2- and 3- substituted 2,3-dihydro-1,4-benzoxathiane scaffolds. After having considered the lack of literature around the chemistry of this heterocycle, we decided to start from an established synthetic method[18], satisfactorily used for the obtainment of a large number of 1,4-benzodioxane derivatives.[19,20]

In particular, as reported in Scheme 2, the desired 1,4-benzodioxane carboxylate was accomplished through condensation of the commercially available catechol with ethyl or methyl 2,3-dibromopropionate, obtained by bromination of the corresponding acrylate.

The mechanism of this reaction was abundantly studied few decades ago firstly by Koo and coworkers[21] and later by Caputo's research group.[22] They strengthened the hypothesis of the initial dehydrobromination of the 2,3-dibromopropionate, achieving the 2-bromoacrylate, and the consecutive Michael addition of the cathecol anion on the primary carbon.

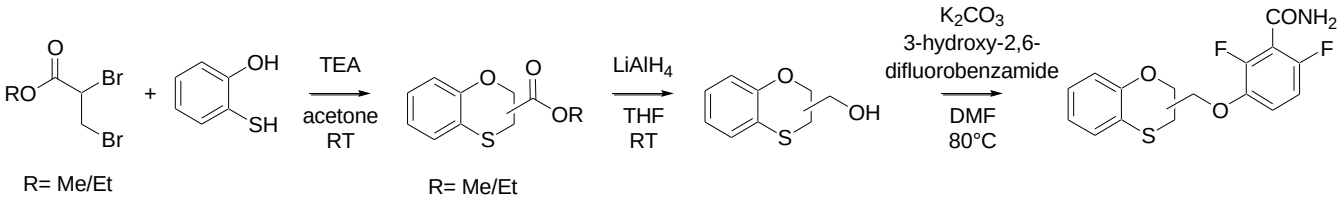
SCHEME 2*: 1,4-benzodioxane scaffold synthesis*



Similarly, considering this simple procedure, we decided to apply it on 1,2-mercaptophenol instead of catechol, treating the 2-hydroxythiophenol with methyl or ethyl 2,3-dibromopropionate, in presence of triethylamine (TEA) as weak organic base.

We aimed at the obtainment of methyl or ethyl 1,4-benzoxathian-2- or 3- carboxylate, which could easily undergo reduction of the estereal function and thus condensation with the suitable phenol, achieving the desired compounds (Scheme 3).

SCHEME 3



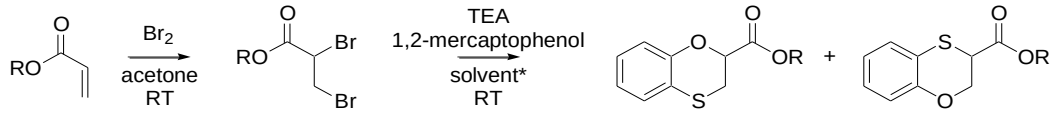
R= Me/Et

R= Me/Et

Results and discussion

We planned to initially use acetone as reaction medium, as previously done for the 1,4-benzodioxane (Scheme 4); interestingly the ^{1}H-NMR of the reaction crude revealed that methyl or ethyl 2,3-dihydro-1,4-benzoxathine-2-carboxylate (**1** and **3**) were almost the single reaction products.

SCHEME 4*: Synthetic pathway for the obtainment of compounds **1/3** and **2/4***



R= Me/Et

Ia (R= Me)
Ib (R= Et)

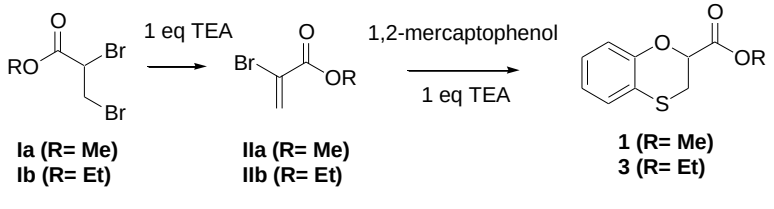
1 (R= Me)
3 (R= Et)

2 (R= Me)
4 (R= Et)

* The solvent used affects regioselectivity

The obtainment of 2- substituted regioisomers **1** and **3** as prevalent products prompted us to outline a hypothetical reaction mechanism (Scheme 5). Thence, we started treating methyl and ethyl dibromopropionate (**Ia** and **Ib**) in acetone with a single equivalent of TEA and we noticed the instant dehydrobromination and the consequent obtainment of methyl or ethyl 2-bromoacrylate (**IIa** and **IIb**). Both the derivatives were easily isolated from the reaction medium and their ^{1}H-NMR[23] spectra confirmed the chemical structure. The second step, consisting in the reaction of **IIa** and **IIb** with 1,2-mercaptophenol and a further equivalent of TEA, probably involves the initial attack of the more nucleophilic thiolate on the β-position. This leads to the achievement of the intermediates **III**, as the main product of the nucleophilic β-addition on the α,β-unsaturated carbonyl function. Unfortunately, we did not succeed in the isolation of intermediates **III** and their characterization, because they rapidly undergo the spontaneous ring closure. This consecutive reaction should be managed by the nucleophilic phenate and further favored by the high electrophilicity of the α-carbon atom, obtaining compounds **1** and **3** as the main regioisomers.

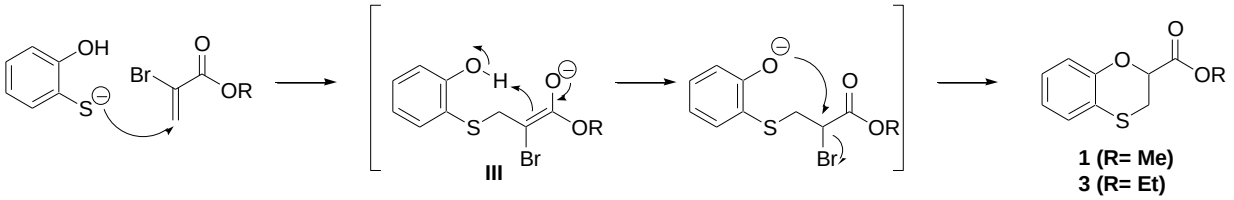
SCHEME 5: *Proposed mechanism of reaction for the obtainment of compounds **1** and **3***



Ia (R= Me)
Ib (R= Et)

IIa (R= Me)
IIb (R= Et)

1 (R= Me)
3 (R= Et)



III

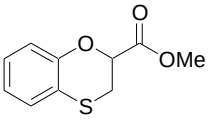
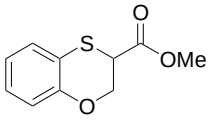
1 (R= Me)
3 (R= Et)

Evaluating how to achieve the regioisomers **2** and **4**, we thought to work on modifying the nucleophile characteristics, trying to avoid substantial changes in the synthetic pathway, as previously we were forced to do for 1,4-benzodioxanes[24, 25, 26] and for the pyrido-dioxanes.[27, 28]

We therefore moved firstly varying the solvent, and secondly evaluating other reaction variables (introduction of co-solvent, changes in reaction temperature and time), in order to understand if the 3- substituted regioisomers could be somehow formed under specific conditions. We highlighted how the solvent change directly affected the achieved regioisomer ratio. In addition, in order to profoundly estimate the composition of each crude, we set up two peculiar HPLC method (see Experimental section for column and methods), able to fully control the reaction conversion and to correctly quantify the regioisomer content.

The most interesting results, here summarized in Tables 1 and 2, highlighted several unexpected features. Besides, we avoided including information on reaction times in the tables, because, after a huge number of attempts, we assessed that the coupling required 72 hours for its completion. No significant changes happened after that period and therefore time has no significant influence on reaction regioselectivity.

*Table 1: Regioisomer percentages of **1** and **2** (evaluated by HPLC), considering the main reaction parameters involved*

Trial	Solvent	Co-solvent	Solvents Ratio	Reaction Temperature	% Regioisomer	
					 1	 2
a-1	DCM	/	100/0	RT	**47%**	**53%**
b-1	Acetone	/	100/0	RT	**94%**	**6%**
c-1	Acetone	/	100/0	60°C	**96%**	**4%**
d-1	ACN	/	100/0	RT	**37%**	**63%**
e-1	ACN	/	100/0	60°C	**16%**	**84%**
f-1	DMF	/	100/0	RT	**51%**	**49%**
g-1	DMF	/	100/0	60°C	**47%**	**53%**
h-1	DMSO	/	100/0	RT	**62%**	**38%**
i-1	DMSO	/	100/0	60°C	**86%**	**14%**

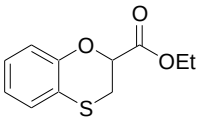
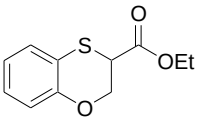
Conversely, we observed how the obtainment of the 2,3-dihydro-1,4-benzoxathiane-2-carboxylates or the 3- substituted ones was completely solvent-dependent, moving from roughly the totality of the 2-substituted regioisomers (**1** and **3**) to an high molar percentage of the 3- substituted derivatives **2** and **4**.

We considered four additional solvents, chosen for their peculiar miscibility with water and for their divergent polarity: dichloromethane (DCM), acetonitrile (ACN), *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).

DCM was firstly used as single solvent and the couplings were performed at RT (***a-1***, ***a-2***), the results were soon significantly different: on one side, the ethyl derivative kept its preference for 2-substitution, showing only 10% of 3- regioisomer. On the other side, the methyl derivative reacted in an opposite way, moving its regioselectivity to an equal proportion of the both products.

The different polarity of methyl and ethyl 2-bromoacrylate prompted us to perform reaction ***b-2*** in an aqueous biphasic system, in the presence of tetrabutylammonium bromide (TBAB) as phase transfer catalysis. In these conditions, the partial formation of the 3-substituted compound **2** was revealed, and its relative abundance was calculated from HPLC analysis and resulted to be of 25%.

*Table 2: Regioisomer percentages of **3** and **4** (evaluated by HPLC), considering the main reaction parameters involved*

Trial	Solvent	Co-solvent	Solvents Ratio	Reaction Temperature	% Regioisomer	
					 3	 4
a-2	DCM	/	100/0	RT	**90%**	**10%**
b-2	DCM	H_2O(+TBAB)	50/50	RT	**75%**	**25%**
c-2	Acetone	/	100/0	RT	**94%**	**6%**
d-2	Acetone	/	100/0	60°C	**96%**	**4%**
e-2	ACN	/	100/0	RT	**76%**	**24%**
f-2	ACN	/	100/0	60°C	**80%**	**20%**
g-2	ACN	H_2O	50/50	RT	**60%**	**40%**
h-2	ACN	H_2O	20/80	RT	**50%**	**50%**
i-2	DMF	/	100/0	RT	**70%**	**30%**
j-2	DMF	/	100/0	60°C	**77%**	**23%**
k-2	DMF	/	100/0	80-90°C	**100%**	**0%**
l-2	DMF	H_2O	50/50	RT	**38%**	**62%**
m-2	DMF	H_2O	20/80	RT	**40%**	**60%**
n-2	DMSO	/	100/0	RT	**71%**	**29%**
o-2	DMSO	/	100/0	60°C	**71%**	**29%**
p-2	DMSO	/	100/0	80-90°C	**100%**	**0%**
q-2	DMSO	H_2O	50/50	RT	**38%**	**62%**
r-2	DMSO	H_2O	20/80	RT	**39%**	**61%**

The scarce results in the obtainment of the 3- substituted regioisomers forced us to consider other solvents, moving to water-miscible ones and with a progressively increased polarity: ACN, DMF, DMSO and water itself.

Acetonitrile was used alone (***d-1*** and ***e-2***) or with growing amounts of water for the ethyl compounds, in order to enhance 3- regioisomer amounts (***g-2***, ***h-2***). The results in Table 1 and Table 2 confirmed that water is crucial in order to enhance the abundance of the 3-substituted derivative and that the maximum reachable size was almost an equimolar ratio of **1/2** and **3/4**. Neither an extreme increase in the quantity of water (***h-2***) has a significant effect on the regioisomer ratio.

DMF afforded progressively upgraded results for ethyl derivatives, reaching almost 60% of derivative **4** when water was added as co-solvent to the reaction medium (***l-2*** and ***m-2***). A similar outcome was achieved using DMSO, whose usage enabled conclusions similar to the DMF ones (***h-1***, ***n-2***, ***q-2*** and ***r-2***).

Furthermore, we evaluated how an increase in the reaction temperature could somehow affect the regioisomer ratio. The results were quite clear for the ethyl derivatives (Table 2); in these trials, the progressive heating of the reaction mixture always moved to an enhancement of the 2- substituted regioisomers. We hypothesized this could be due to a thermo-dependent stabilization of the intermediate **III**.

A different behavior was observed for the methyl compounds, which regioisomer preference at high temperature was completely solvent-dependent.

The interesting results highlighted how the regioisomer balance was severely solvent-dependent, and particularly how the more polar was the solvent used the more profuse was the amount of the 3-substituted compound yielded. Indeed, the addition of water as co-solvent moved to a strong redefinition of the balance between **3** and **4**.

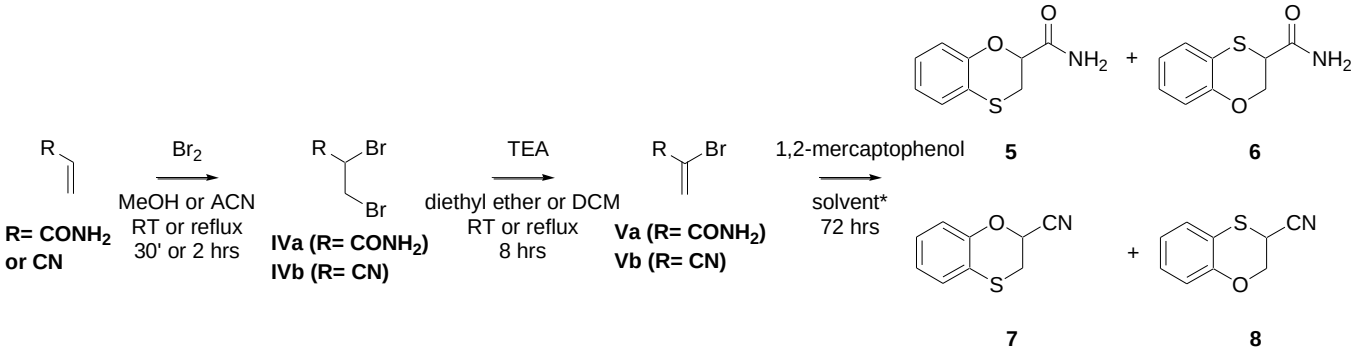
Unfortunately, the water insolubility of both the reagents and the reaction products prevented the possibility of using pure water as the reaction solvent. This prompted us to consider other water-soluble 1,2-dibromo-moieties and to deeply examine their influence on the regioselectivity balance, while using the best reaction conditions seen by far.

We therefore moved to the application of the same synthetic procedure over two more polar scaffolds, thus starting from 2,3-dibromopropionamide (**IVa**) and 2,3-dibromoproprionitrile (**IVb**), following the same synthetic pathway of the two estereal series, starting from the commercial acrylamide and acrylonitrile, as shown in Scheme 6.

The bromine addition on the acrylamide or the acrylonitrile afforded derivatives **IV** in good to quantitative yields, and was followed by treatment with 1 equivalent of TEA, causing the complete

dehydrobromination and the obtainment of compounds **Va** and **Vb** that were isolated and fully characterized.

SCHEME 6: *Synthetic pathway for the obtainment of compounds **5/8***



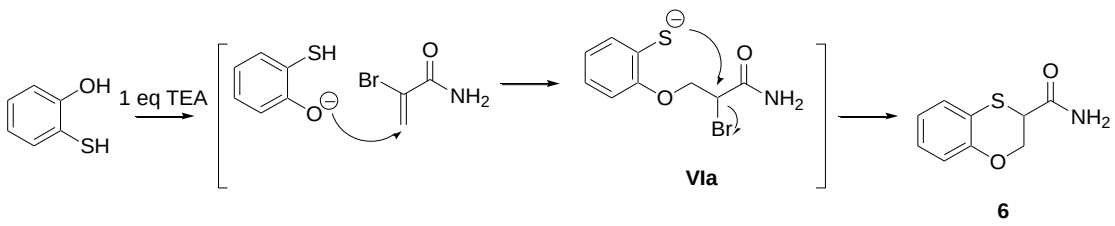
* The solvent used affects the regioselectivity

The modest to high solubility of compounds **V** in water let to accomplish the coupling reaction in pure water (***f-3*** and ***f-4***).

Interestingly and unexpectedly, working on the amide (***f-3***), operating at room temperature, and stirring for 72 hours, as done before, we had the complete conversion and the obtainment of a single derivative; ^{1}H and ^{13}C NMR confirmed its nature as the 3-substituted regioisomer **6**. We did not evaluated any trace of the 2-substituted compound **5**, neither in TLC nor in NMR spectra and in HPLC (see Experimental section for column and methods).

Here, the proposed reaction mechanism is similar to the one presented in Scheme 4, but in this case, TEA mediates the initial deprotonation of the phenolic function (see Scheme 7). The resulting phenate is the nucleophile directly responsible of the attack on the double bond and the consecutive achievement of Intermediate **VIa**. Contrarily to what observed for Intermediate **III**, we succeeded in the isolation of this derivative by blocking the reaction after a few hours. Unfortunately, the chromatography required for its characterization was truly demanding and we obtained Intermediate **VIa** in poor yield and slightly poisoned by the presence of 1,2-mercaptophenol; nevertheless the ^{1}H NMR confirmed its structure.[29] In order to further verify its identity, we successively treated isolated Intermediate **VIa** with a further equimolar amount of TEA, leading to the complete conversion into the desired derivative **6**.

SCHEME 7: *Proposed mechanism of reaction for the obtainment of compound **6***

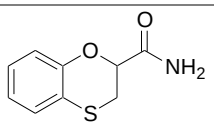
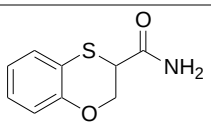


Here, the possibility to isolate Intermediate **VIa** could be explained on one hand by the lower electrophilicity of the amide α-carbon atom, and on the other by the reduced basic properties in the aqueous medium, slowing down the spontaneous ring closure, achieving the 3-substituted benzoxathiine **6**.

In addition to water, we evaluated the same solvents used before for the esters, starting from Intermediate **Va**. Contrarily to what seen for esters **1**/**2** and **3**/**4**, the condensation performed in pure DCM (***a-3***) and using the reaction parameters set before (RT, 72 hours reaction time) let to the obtainment of both **5** and **6**. We quantified the regioisomer balance by HPLC and it resulted to be of 34% **5** vs 66% **6**, as reported in Table 3.

The use of acetone (***b-3***) or ACN (***c-3***) had a similar outcome, with a final almost equimolar amount of **5** and **6**. Furthermore, neither DMF nor DMSO revealed to be good solvents for these amides because their use limited the 1,4-benzoxatine ring formation and the reaction mixture revealed to be composed mainly of 1,2-mercaptophenol. Consequently, for these derivatives, the presence of both the regioisomers suggested how both the substrate and the solvent polarities have a key role in the reaction.

*Table 3: Regioisomer percentages of **5** and **6** (evaluated by HPLC), considering the main reaction parameters involved*

	SOLVENT	CO-SOLVENT	Solvents Ratio	Reaction Temperature	% Regioisomers	
					 5	 6
a-3	DCM	/	100/0	RT	**34%**	**66%**
b-3	Acetone	/	100/0	RT	**42%**	**58%**
c-3	ACN	/	100/0	RT	**50%**	**50%**
d-3	DMF	/	100/0	RT	**nd**	**nd**
e-3	DMSO	/	100/0	RT	**nd**	**nd**
f-3	H_2O	/	100/0	RT	**0%**	**100%**

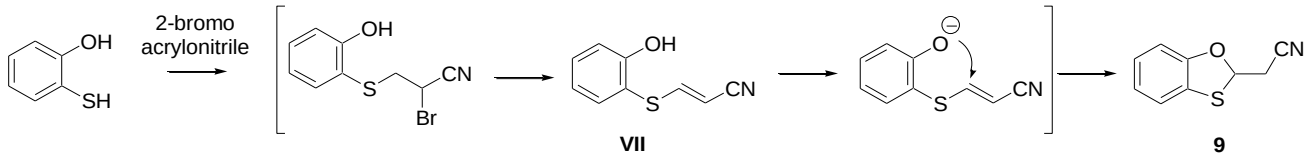
Differently, working in water on the 2-bromoacrylonitrile (***f-4***, Table 4), operating at room temperature, and stirring for 72 hours, as done before, we did not have the complete conversion of the 1,2-mercaptophenol into one or both the regioisomers.

Even if both **7** and **8** were partially achieved, a novel and structurally different derivative revealed to be the main reaction product (reaching yields of 87% when performing the reaction in acetone – ***b-3***). We then isolated the compound by flash chromatography and analyzed it through NMR: ^1H

and ^{13}C spectra confirmed its nature as the 1,3-benzoxathiol-2-acetonitrile **9**. The same derivative, even if achieved with lower amounts, was the main product of all the reactions.

Here, we proposed a different reaction mechanism, coming from the results reached by Cabiddu and coworkers a few decades ago[30] (See Scheme 8).

SCHEME 8: *Proposed mechanism of reaction for the obtainment of compound **9***

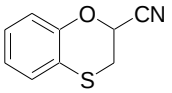
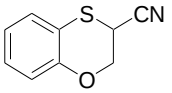


VII **9**

Specifically, the 2-bromoacrylonitrile **Vb** underwent Michael reaction on the 1,2-mercaptophenol followed by dehydroalogenation, achieving Intermediate **VII**. This intermediate was sequentially deprotonated by TEA on its phenolic function.

The resulting phenate is directly responsible of the closure of the ring, achieving **9**.

*Table 4: Regioisomer percentages of **7** and **8** (evaluated by HPLC), considering the main reaction parameters involved. (*The relative percentages do not consider the formation of the 1,3-benzoxathiol **9**)*

	SOLVENT	CO-SOLVENT	Solvents Ratio	Reaction Temperature	% Regioisomers	
						
					7	8
a-4	DCM	/	100/0	RT	**85%***	**15%***
b-4	Acetone	/	100/0	RT	**56%***	**44%***
c-4	ACN	/	100/0	RT	**37%***	**63%***
d-4	DMF	/	100/0	RT	**51%***	**49%***
e-4	DMSO	/	100/0	RT	**62%***	**38%***
f-4	H_2O	/	100/0	RT	**33%***	**67%***

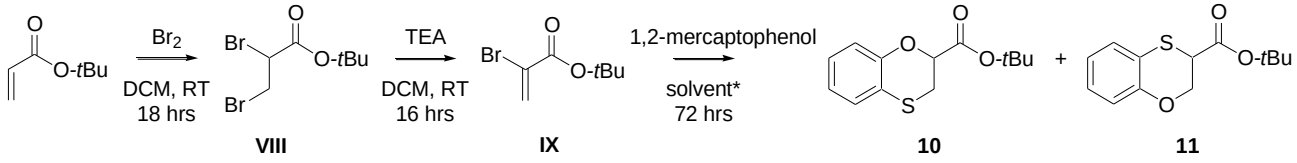
Despite the interesting result of this unknown 5-membered ring, the presence of both the regioisomers in all the tested solvents (***a-4***-***e-4***, Table 4) stressed once again the importance of both the substrate and the solvent polarities in the regioisomer selection.

Consequently, we decided to further enlarge the scope of this reaction, evaluating an additional starting material that shows a substantial increase in lipophilicity: the *tert*-butyl acrylate. We aimed at better understanding how such a lipophilic change could affect the regioisomer balance when applying the previously set-up reaction conditions.

We therefore started quantitatively preparing the *tert*-butyl 2-bromoacrylate (**IX**) through the formation of the intermediate *tert*-butyl 2,3-dibromopropionate **VIII**, as previously described for the

other derivatives. Both **VIII** and **IX** were isolated, fully characterized and compared with literature data,[31] in order to assess their structure identities (Scheme 9).

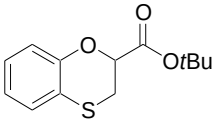
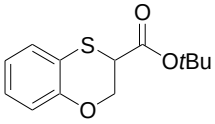
SCHEME 9: *Synthetic pathway for the obtainment of compounds **10/11***



* The solvent used affects the regioselectivity

The lipophilic properties of compound **IX** let to accomplish the coupling reaction in DCM, acetone, ACN, DMF and DMSO, as done for the previous derivatives (***a-5*** to ***e-5*** in Table 5), while its insolubility in water required an aqueous biphasic system, as in ***b-2***, by adding tetrabutylammonium bromide (TBAB) as phase transfer catalysis.

*Table 5: Regioisomer percentages of **10** and **11** (evaluated by HPLC), considering the main reaction parameters involved. (*The relative percentages do not consider the formation of the tert-butyl-α-(2-hydroxyphenyl)thio-acrylate **12**)*

	SOLVENT	CO-SOLVENT	Solvents Ratio	Reaction Temperature	% Regioisomers	
					 10	 11
a-5	DCM	/	100/0	RT	**36%***	**64%***
b-5	Acetone	/	100/0	RT	**73%***	**27%***
c-5	ACN	/	100/0	RT	**32%***	**68%***
d-5	DMF	/	100/0	RT	**15%***	**85%***
e-5	DMSO	/	100/0	RT	**41%***	**59%***
f-5	H_2O	DCM (+ TBAB)	50/50	RT	**24%***	**76%***

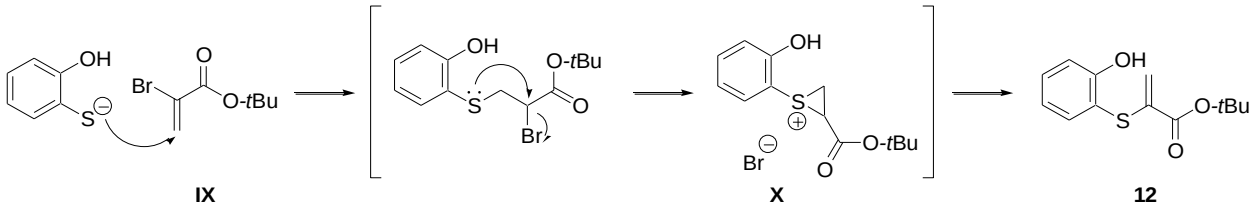
Unexpectedly, working with the *tert*-butyl derivative at room temperature and stirring for 72 hours, as done before, we did not completely converted the 1,2-mercaptophenol into one or both the regioisomers. Hence, together with the partial obtainment of both **10** and **11**, we identified an additional and unfamiliar reaction product, which was achieved with different yields (from traces amounts in acetone- ***b-5*** up to main product in ACN- ***c-5***) depending on the solvent used.

As previously done for derivative **9**, we isolated the novel compound by flash chromatography and we analyzed it through NMR. ^{1}H and ^{13}C spectra helped us in defining its nature as the *tert*-butyl-α-(2-hydroxyphenyl)thio-acrylate **12**.

Starting from the structure of this novel compound, we hypothesized that, after the initial Michael addition of the thiolate on the 2-bromo acrylate, an intramolecular cyclization to bromine-solfonium salt **X** took place, driven by the steric hindrance of the *tert*-butyl group (Scheme 10).

Intermediate **X** is completely unstable and soon rearranged to the olefinic thio-derivative **12**; a similar outcome was already seen by Boucher and collaborators,[32] while working on the synthesis of differently hindered dienophilic olefins.

SCHEME 10: *Proposed mechanism of reaction for the obtainment of compound **12***



The impressive and unpredictable results coming from the different substrates corroborated our hypothesis in considering of equal importance in the regioisomer selection both the substrate and the solvent features.

Conclusion

In conclusion, we found a completely innovative and easy method for the obtainment of pure 2-, pure 3- or a differently proportioned mixture of 2- and 3- substituted 2,3-dihydro-1,4-benzoxathiine. With the present work we demonstrated how the regioselectivity of this scaffold could be strongly dependent on the polarity of the reaction medium as well as on the nature of the reagents employed.

In particular, in our opinion, the negative charge, due to deprotonation, moves from phenol, in polar solvents, to thiol, in non-polar ones. The whole molecule becomes more polar in the presence of the phenolate; by contrast, in non-polar solvents the deprotonation is transferred to the thiolate, making the complete molecule more lipophilic.

Furthermore, each single structural feature of the reactives, in particular the polarity, the water solubility and the steric hindrance, have an exclusive, noteworthy and additive effect on the final regioisomer balance.

Experimental section:

General:

Ethyl acrylate, methyl acrylate, acrylonitrile, acrylamide and *tert*-butyl acrylate were purchased from commercial suppliers and were used without further purification. The solvents, such as acetone, DCM, DMF, DMSO, analytical grade ACN, were purchased from Sigma Aldrich. ^{1}H and ^{13}C NMR spectra were taken on Varian 300 Mercury NMR spectrometer operating at 300 MHz for ^{1}H NMR, and 75 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in ppm relative to residual solvent as internal standard. Signal multiplicity is used according to the following abbreviations: s= singlet, d= doublet, dd= doublet of doublets, t=triplet, td= triplet of doublets, q=quadruplet, m=multiplet, sept= septuplet and bs= broad singlet. Elemental analyses of the new substances are within 0.40 % of theoretical values. Silica gel F_{254} was used in analytical thin-layer chromatography (TLC), and silica gel (particle size 40-63 µm, Merck) was used in flash chromatography; visualizations were accomplished with UV light (λ 254 nm). Melting point were determined by DSC (TA INSTRUMENTS) or Büchi Melting Point (B-540).

The regioisomer-separation analyses were performed on HPLC by using Elite LaChrom HPLC system with diode array detector (190–400 nm) and a Water XBridgeTM C-18 column (5 µm, 4.6x150mm). The peculiar methods (A, B, C and D) are reported in the Supporting Information and proved to be effective in separating all the regioisomeric pairs of the final compounds.

HPLC evaluation:

The HPLC methods were set up, using a Water XBridgeTM C-18 column, which was flushed with freshly prepared acetate buffer (pH 4.7)/ACN (70:30, v/v) for **1**/**2**, **5**/**6** and **7**-**9**, acetate buffer (pH 4.7)/ACN (65:35, v/v) for **3/4** or acetate buffer (pH 4.7)/ACN (60:40, v/v) for **10**-**12**, until column pressure was stable.

All the investigated samples were prepared through dissolution either of the crude reaction mixtures or of the purified products in the selected mobile phase, at the approximate concentrations of 1 mg/mL, filtered through a 0.45 µm filter and analyzed. The injection volume was 20 µL. Owing to the presence of the 1,4-benzoxathiane or the 1,3-benzoxathiol scaffold in each compound, regioisomer contents were evaluated on chromatograms recorded at 290 nm.

Synthesis:

Methyl 2,3-dibromopropionate[33] **(Ia).** Bromine (0.57 mL, 11.1 mmol) was added dropwise to a solution of methyl acrylate (1.0 mL, 11.1 mmol) in acetone (10 mL), under reflux. Once added, the reaction mixture was kept stirring at reflux for 30 minutes. The reaction mixture was then brought

to room temperature, quenched with aqueous 10% sodium thiosulfate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording **Ia** as a colourless oil. Yield: 2.42 g (89%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 4.45 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.92 (dd, *J* = 11.3, 9.9 Hz, 1H), 3.84 (s, 3H), 3.68 ppm (dd, *J* =9.9, 4.4 Hz, 1H). Anal. Calcd for $C_4H_6Br_2O_2$: C, 19.54; H, 2.46; Br, 64.99; O, 13.01. Found: C, 19.12; H, 2.66; Br, 65.23; O, 12.98.

Methyl 2-bromoacrylate[34] **(IIa).** TEA (1.13 mL, 8.13 mmol) was added dropwise to a solution of **Ia** (2.0 g, 8.13 mmol) in acetone (10 mL), at room temperature. Once added, the reaction mixture was stirred for 30 minutes at room temperature and filtered. The resulting solution was washed with aqueous 10% HCl solution, dried over Na_2SO_4, filtered and concentrated, affording **IIa** as a yellow oil. Yield: 1.34 g (99%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.97 (d, *J* = 1.6 Hz, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 3.85 ppm (s, 3H). Anal. Calcd for $C_4H_5BrO_2$: C, 29.12; H, 3.05; Br, 48.43; O, 19.39. Found: C, 28.96; H, 3.08; Br, 48.78; O, 19.18.

General procedure for Methyl 1,4-benzoxathian-2-carboxylate (1) or Methyl 1,4-benzoxathian-3-carboxylate (2): TEA (0.25 mL, 1.76 mmol) was added dropwise to a solution of **Ia** (0.22 g, 0.88 mmol) into the desired solvent (4 mL). Compound **IIa** was quantitatively accomplished after stirring at room temperature for 30 min, therefore 1,2-mercaptophenol (0.11 g, 0.88 mmol) was slowly added. The reaction mixture was stirred at RT or at 60°C for 72 hrs, then it was diluted with diethyl ether and water, the organic phase was dried over Na_2SO_4, filtered and concentrated, to give a yellow oil as residue. The crude was purified by flash chromatography on silica gel, using cyclohexane/ethyl acetate 9/1 as elution solvent, the yielded ratio between the two regioisomers was quantified by ^{1}H NMR and HPLC data. Global yield: from 0.08 g (43%) to 0.15 g (80%), depending on the solvents used.

Methyl 1,4-benzoxathian-2-carboxylate (1): yellowish oil, t_r (Method A): 17.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.05 (m, 2H), 6.97 (dd, *J*= 8.7, 1.2 Hz, 1H), 6.88 (dd, *J*= 7.4, 1.2 Hz, 1H), 5.03 (dd, *J* = 4.8, 3.9 Hz, 1H), 3.82 (s, 3H), 3.29 (d, *J* = 3.9 Hz, 1H), 3.28 ppm (d, *J* = 4.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=169.2, 150.2, 127.6, 126.3, 121.9, 118.5, 116.5, 72.7, 52.8, 26.7. Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; O, 22.83; S, 15.25. Found: C, 57.41; H, 4.59; O, 22.63; S, 15.36.

Methyl 1,4-benzoxathian-3-carboxylate (2): colourless oil, t_r (Method A): 18.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.05 (m, 2H), 6.89 (m, 2H), 4.55 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.49 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.14 (dd, *J* = 5.9, 3.3 Hz, 1H), 3.81 ppm (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=169.0, 151.0, 127.0, 125.9, 122.1, 118.4, 116.6, 65.9, 53.1, 41.3. Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; O, 22.83; S, 15.25. Found: C, 57.39; H, 4.63; O, 22.68; S, 15.30.

Ethyl 2,3-dibromopropionate[35] **(Ib).** Bromine (0.51 mL, 10.0 mmol) was added dropwise to a solution of ethyl acrylate (1.0 g, 10.0 mmol) in acetone (10 mL), under reflux. Once added, the reaction mixture was kept stirring at reflux for 30 minutes. The reaction mixture was then brought to room temperature, quenched with aqueous 10% sodium thiosulfate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording **Ib** as a yellowish oil. Yield: 2.60 g (100%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 4.42 (dd, *J* = 11.4, 4.4 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.67 (dd, J = 9.9, 4.4 Hz, 1H), 1.32 ppm (t, *J* = 7.1 Hz, 3H). Anal. Calcd for $C_5H_8Br_2O_2$: C, 23.10; H, 3.10; Br, 61.48; O, 12.31. Found: C, 22.92; H, 3.01; Br, 61.63; O, 12.44.

Ethyl 2-bromoacrylate[36] **(IIb).** TEA (0.18 mL, 1.27 mmol) was added dropwise to a solution of **Ib** (0.3 g, 1.15 mmol) in acetone (3 mL), at room temperature. Once added, the reaction mixture was stirred for 30 minutes at room temperature and filtered. The resulting solution was washed with aqueous 10% HCl solution, dried over Na_2SO_4, filtered and concentrated to dryness, affording **IIb** as a yellow oil. Yield: 0.20 g (97%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.95 (s, 1H), 6.26 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 ppm (t, *J* = 7.1 Hz, 3H). Anal. Calcd for $C_5H_7BrO_2$: C, 33.55; H, 3.94; Br, 44.64; O, 17.88. Found: C, 33.36; H, 3.88; Br, 44.83; O, 17.92.

General procedure for Ethyl 1,4-benzoxathian-2-carboxylate (3) or Ethyl 1,4-benzoxathian-3-carboxylate (4): 3 and **4** were accomplished starting from **Ib** (0.23 g, 0.88 mmol) and 1,2-mercaptophenol (0.11 g, 0.88 mmol), following the same procedure described for **1** and **2**, and purifying the products by flash chromatography on silica gel, using cyclohexane/ethyl acetate 95/5 as elution solvent. The ratio between the two regioisomers was quantified by ^{1}H NMR and HPLC data; global yield: 0.11 g (54%) to 0.16 g (80%), depending on the solvent used.

Ethyl 1,4-benzoxathian-2-carboxylate (3): yellow oil, t_r (Method B): 22.3 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.04 (m, 2H), 6.96 (d, *J*= 7.7 Hz, 1H), 6.87 (t, *J*= 7.4 Hz, 1H), 4.99 (dd, *J* = 5.3, 3.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.29 (d, *J* = 3.8 Hz, 1H), 3.28 (d, *J* = 5.3 Hz, 1H), 1.28 ppm (t, *J*= 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=168.7, 150.3, 127.5, 126.2, 121.8, 118.5, 116.5, 72.5, 61.9, 26.7, 14.1. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; O, 21.40; S, 14.30. Found: C, 58.61; H, 5.59; O, 21.63; S, 14.17.

Ethyl 1,4-benzoxathian-3-carboxylate (4): yellow oil, t_r (Method B): 24.3 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.06 (m, 1H), 7.00 (dd, *J*= 7.6, 2.0 Hz, 1H), 6.88 (t, *J*= 7.4 Hz, 2H), 4.56 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.46 (dd, *J* = 11.5, 6.5 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.12 (dd, *J* = 6.5, 3.0 Hz, 1H), 1.30 ppm (t, *J*= 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=168.5, 151.1, 127.0, 125.9, 122.0, 118.4, 116.8, 66.1,

62.2, 41.4, 14.1. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; O, 21.40; S, 14.30. Found: C, 58.58; H, 5.71; O, 21.63; S, 14.08.

2,3-dibromopropionamide[37] **(IVa).** Bromine (1.44 mL, 28.14 mmol) was added dropwise to a solution of acrylamide (2.0 g, 28.14 mmol) in methanol (12 mL), at room temperature. Once added, the reaction mixture was refluxed for 30 minutes, until decoloration occurred, then concentrated to dryness, affording **IVa** as a white solid. Yield: 6.50 g (100%). MP= 111°C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.12 (bs, 1H), 6.00 (bs, 1H), 4.49 (dd, *J* = 8.5, 4.6 Hz, 1H), 3.95 (dd, *J* = 10.4, 8.5 Hz, 1H), 3.81 ppm (dd, *J* = 10.4, 4.6 Hz, 1H). Anal. Calcd for $C_3H_5Br_2NO$: C, 15.61; H, 2.18; Br, 69.22; N, 6.07; O, 6.93. Found: C, 15.75; H, 2.42; Br, 69.01; N, 6.13; O, 6.69.

2-bromoacrylamide[38] **(Va).** TEA (2.41 mL, 17.32 mmol) was added dropwise to a solution of **IVa** (4.0 g, 17.32 mmol) in diethyl ether (40 mL), at room temperature. Once added, the reaction mixture was refluxed for 80 hrs, the resulting suspension was filtered and the filtrate concentrated to dryness, affording **Va** as a yellowish wax. Yield: 2.35 g (90%).**^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.96 (s, 1H), 6.52 (bs, 1H), 6.06 ppm (s, 1H), 5.90 (bs, 1H). Anal. Calcd for C_3H_4BrNO: C, 24.03; H, 2.69; Br, 53.28; N, 9.34; O, 10.67. Found: C, 24.14; H, 2.92; Br, 53.03; N, 9.07; O, 10.84.

General procedure for 1,4-benzoxathian-2-carboxamide (5) or 1,4-benzoxathian-3-carboxamide (6): 5 and **4** were accomplished starting from **IVa** (0.20 g, 0.88 mmol) and 1,2-mercaptophenol (0.11 g, 0.88 mmol), following the same procedure described for **1** and **2**, and purifying the products by flash chromatography on silica gel, using cyclohexane/ethyl acetate 1/1 as elution solvent. The ratio between the two regioisomers was quantified by ^{1}H NMR data; global yield: 0.012 g (7%) to 0.13 g (75%), depending on the solvent used.

1,4-benzoxathian-2-carboxamide (5): yellow oil, t_r (Method C): 7.6 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.12–6.97 (m, 2H), 6.89 (m, 2H), 6.61 (bs, 1H), 6.39 (bs, 1H), 4.73 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.36 (dd, *J* = 13.2, 2.5 Hz, 1H), 3.19 ppm (dd, *J* = 13.2, 8.4 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ= 171.3, 149.9, 127.8, 126.1, 122.4, 118.2, 117.9, 74.4, 27.1. Anal. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17; O, 16.39; S, 16.42. Found: C, 55.61; H, 4.58; N, 6.97; O, 16.59; S, 16.25.

1,4-benzoxathian-3-carboxamide (6): white solid, MP:124°C, t_r (Method C): 6.4 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.05 (m, 2H), 6.91 (t, *J* = 8.2 Hz, 2H), 6.81 (bs, 1H), 6.24 (bs, 1H), 4.91 (dd, *J* = 11.4, 3.3 Hz, 1H), 4.21 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.89 ppm (dd, *J* = 3.3, 2.0 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ= 171.1, 151.6, 127.0, 126.3, 122.4, 119.0, 115.1, 66.0, 42.6. Anal. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17; O, 16.39; S, 16.42. Found: C, 55.65; H, 4.51; N, 7.07; O, 16.50; S, 16.27.

2,3-dibromopropionitrile[39] **(IVb).** Bromine (0.96 mL, 18.8 mmol) was added dropwise to a solution of acrylonitrile (1.0 g, 18.8 mmol) in ACN (10 mL), at 0-5 °C. Once added, the reaction mixture was warmed to RT and stirred for 2 hours. The reaction mixture was then diluted with DCM (20 mL) and quenched with aqueous 10% sodium thiosulfate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording **IVb** as a yellowish oil. Yield: 2.42 g (60%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 4.54 (dd, *J* = 9.2, 6.3 Hz, 1H), 3.78 (d, *J* = 9.2 Hz, 1H), 3.78 ppm (d, *J* = 6.3 Hz, 1H). Anal. Calcd for $C_3H_3Br_2N$: C, 16.93; H, 1.42; Br, 75.07; N, 6.58. Found: C, 16.72; H, 1.71; Br, 75.23; N, 6.34.

2-bromoacrylonitrile[39] **(Vb).** TEA (1.59 mL, 11.39 mmol) was added dropwise to a solution of **IVb** (2.43 g, 11.39 mmol) in DCM (20 mL), at room temperature. Once added, the reaction mixture was stirred for 3 hours at room temperature and filtered. The resulting solution was washed with aqueous 10% HCl solution, dried over Na_2SO_4, filtered and concentrated to dryness, affording **Vb** as a yellow oil. Yield: 1.19 g (78%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.72 (d, *J* = 2.4 Hz, 1H), 6.41 ppm (d, *J* = 2.4 Hz, 1H). Anal. Calcd for C_3H_2BrN: C, 27.31; H, 1.53; Br, 60.55; N, 10.61. Found: C, 27.13; H, 1.48; Br, 60.76; N, 10.63.

General procedure for 1,4-benzoxathian-2-carbonitrile (7) or 1,4-benzoxathian-3-carbonitrile (8): **7** and **8** were accomplished starting from **IVb** (0.19 g, 0.88 mmol) and 1,2-mercaptophenol (0.11 g, 0.88 mmol), following the same procedure described for **1** and **2**, and purifying the products by flash chromatography on silica gel, using cyclohexane/ethyl acetate 9/1 as elution solvent. The ratio between the two regioisomers was quantified by ^{1}H NMR and HPLC data; global yield: 0.020 g (13%) to 0.093 g (60%), depending on the solvent used.

1,4-benzoxathian-2-carbonitrile (7): yellow oil, t_r (Method A): 17.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.08 (m, 2H), 6.94 (m, 2H), 5.33 (dd, *J*= 5.7, 2.9 Hz, 1H), 3.40 (dd, *J* = 13.6, 2.9 Hz, 1H), 3.28 ppm (dd, *J* = 13.6, 5.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ= 148.6, 127.7, 126.6, 123.2, 118.9, 116.2, 115.7, 62.7, 27.9. Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90, O, 9.03; S, 18.09. Found: C, 61.27; H, 3.79; N, 7.82, O, 9.22; S, 17.89.

1,4-benzoxathian-3-carbonitrile (8): white solid, MP: 68.5°C, t_r (Method A): 13.6 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.09 (m, 2H), 6.96 (m, 2H), 4.69 (dd, *J* = 11.5, 4.1 Hz, 1H), 4.35 (dd, *J* = 11.5, 2.2 Hz, 1H), 4.14 ppm (dd, *J* = 4.1, 2.2 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=150.2, 127.1, 127.0, 122.8, 119.0, 116.5, 113.7, 65.7, 26.8. Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90, O, 9.03; S, 18.09. Found: C, 61.37; H, 3.75; N, 7.73, O, 9.21; S, 17.94.

1,3-Benzoxathiol-2-yl-acetonitrile (9): yellow oil, t_r (Method A): 13.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.18 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.07 (m, 1H), 6.97 (d, *J*= 7.5, 1.3 Hz, 1H), 6.90 (m, 1H), 6.23 (t, *J*= 5.7 Hz, 1H), 3.05 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.96 ppm (dd, *J* = 16.8, 5.5 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ=154.1, 126.6, 123.6, 123.2, 122.3, 115.2, 111.0, 85.6, 27.1. Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90, O, 9.03; S, 18.09. Found: C, 61.08; H, 3.89; N, 7.62, O, 9.02; S, 18.39.

***Tert*-Butyl 2,3-dibromopropionate**[31] **(VIII).** Bromine (0.40 mL, 7.8 mmol) was added dropwise to a solution of *tert*-butyl acrylate (1.14 mL, 7.8 mmol) in DCM (10 mL), at 0-5 °C. Once added, the reaction mixture was warmed to RT and stirred for 18 hours. The reaction mixture was then diluted with DCM (20 mL) and quenched with aqueous 10% sodium thiosulfate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording **VIII** as a colourless oil. Yield: 2.25 g (quantitative). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 4.33 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.88 (dd, *J* = 11.4, 9.7 Hz, 1H), 3.64 (dd, *J* = 9.7, 4.4 Hz, 1H), 1.51 ppm (s, 9H). Anal. Calcd for $C_7H_{12}Br_2O_2$: C, 29.20; H, 4.20; Br, 55.49; O, 11.11. Found: C, 29.42; H, 4.07; Br, 55.37; O, 11.13.

***Tert*-Butyl 2-bromoacrylate**[31] **(IX).** TEA (1.09 mL, 7.80 mmol) was added dropwise to a solution of **VIII** (2.25 g, 7.80 mmol) in DCM (20 mL), at room temperature. Once added, the reaction mixture was stirred for 16 hours at room temperature and filtered. The resulting solution was washed with aqueous 10% HCl solution, dried over Na_2SO_4, filtered and concentrated to dryness, affording **IX** as a yellowish oil. Yield: 1.53 g (95%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 6.85 (d, *J* = 1.5 Hz, 1H), 6.21 (d, *J* = 1.5 Hz, 1H), 1.51 ppm (s, 9H). Anal. Calcd for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35; Br, 38.59; O, 15.45. Found: C, 40.79; H, 5.42; Br, 38.46; N, 15.33.

General procedure for *tert*-Butyl 1,4-benzoxathian-2-carboxylate (10) or *tert*-Butyl 1,4-benzoxathian-3-carboxylate (11): 10 and **11** were accomplished starting from **VIII** (0.25 g, 0.88 mmol) and 1,2-mercaptophenol (0.11 g, 0.88 mmol), following the same procedure described for **1** and **2**, and purifying the products by flash chromatography on silica gel, using cyclohexane/ethyl acetate 98/2 as elution solvent. The ratio between the two regioisomers was quantified by ^{1}H NMR and HPLC data; global yield: 0.066 g (30%) to 0.18 g (80%), depending on the solvent used.

***Tert*-Butyl 1,4-benzoxathian-2-carboxylate (10):** white wax, t_r (Method D): 30.8 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.04 (m, 2H), 6.95 (m, 1H), 6.86 (m, 1H), 4.93 (dd, *J*= 5.2, 3.2 Hz, 1H), 3.29 (dd, *J* = 13.1, 3.2 Hz, 1H), 3.23 (dd, *J* = 13.1, 5.2 Hz, 1H), 1.47 ppm (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ= 167.7, 150.3, 127.5, 126.2, 121.6, 118.4, 116.5, 82.8, 72.3, 27.9, 26.7. Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; O, 19.02; S, 12.71. Found: C, 61.57; H, 6.54; O, 19.22; S, 12.67.

***Tert*-Butyl 1,4-benzoxathian-3-carboxylate (11):** cream oil, t_r (Method D): 38.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.04 (m, 2H), 6.95 (m, 1H), 6.86 (m, 1H), 4.56 (dd, *J*= 11.5, 2.9 Hz, 1H), 4.39 (dd, *J* = 11.5, 6.9 Hz, 1H), 4.05 (dd, *J* = 6.9, 2.9 Hz, 1H), 1.48 ppm (s, 9H).**^{13}C NMR (75 MHz, $CDCl_3$):** δ=167.5, 151.1, 129.8, 127.0, 125.7, 121.9, 118.3, 83.0, 66.3, 42.3, 27.9. Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; O, 19.02; S, 12.71. Found: C, 61.61; H, 6.51; O, 19.26; S, 12.61.

***Tert*-Butyl α-(2-hydroxyphenyl)thio-acrylate (12)**: colourless oil, t_r (Method D): 24.2 min. **^{1}H NMR (300 MHz, $CDCl_3$):** δ= 7.45 (dd, *J*= 7.7, 1.6 Hz, 1H), 7.37 (m, 1H), 7.06 (dd, *J*= 8.2, 1.3 Hz, 1H), 6.95 (dd, *J*= 7.7, 1.3 Hz, 1H), 6.51 (bs, 1H), 6.22 (s, 1H), 5.07 (s, 1H), 1.53 ppm (s, 9H).**^{13}C NMR (75 MHz, $CDCl_3$):** δ=163.1, 157.2, 137.9, 136.7, 132.5, 121.6, 121.4, 115.8, 115.0, 83.0, 27.9. Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; O, 19.02; S, 12.71. Found: C, 61.59; H, 6.60; O, 19.20; S, 12.60.

Supporting information

^{1}H NMR of all the compounds, ^{13}C NMR spectra of the derivatives **1**-**12**, COSY NMR of Intermediate **VIa** (together with their nomenclature and their chemical structure) and HPLC methods.

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