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Metathetic sulfur transfer mediated by *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione derivatives. Part III: an alkylthiol- and thioacid-free route to diversely substituted *S*-alkyl thioesters

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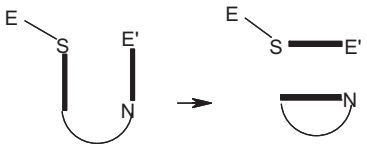
ABSTRACT

A metal free synthesis of *S*-alkyl thioesters, which does not involve alkylthiol or thiocarboxylic acid as sulfur source is disclosed. The process involves first an acylation at the nitrogen of the readily available *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione, second an alkylation at sulfur of the resulting amides and finally a base catalyzed metathetic reaction, which provides under very mild conditions and in high isolated yields the *S*-alkyl thioesters. An ion-pair intermediate (9-acyl-3-methyl[1,3]thiazolo[3,2-*a*][3,1]benzimidazol-9-ium alkylthiolate) accounts for the formation of mixed thioesters during cross-coupling experiments.

S-Alkyl diversity is provided by the alkylating agent and the acyl diversity comes from the acylating agent, while the sulfur atom is provided by the heterocycle.

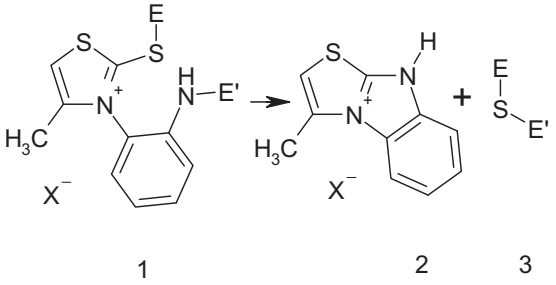
1. Introduction

We are currently exploring the scope of a general methodology in which a sulfur atom is cleanly and quantitatively inserted between two electrophilic residues E and E′. The metathetic sulfur transfer process is cartooned in Scheme 1.



Scheme 1.

Chemistry corresponding to Scheme 1 was shown to proceed nicely when one starts from the heterocyclic salt **1**, which decomposes under mild basic conditions to yield a thiazolobenzimidazolium salt **2** and an organo-sulfur derivative **3** (Scheme 2).



Scheme 2.

Some years ago, our interest was mainly focused on a new route to prepare diversely substituted thiazolo[3,2-*a*]benzimidazole derivatives **2** from the corresponding thiazolium salts **1** (E=Me and E′=H). In the reported examples, CH_3SH was the by-product **3**, which was produced in stoichiometric amount and was readily eliminated from the reaction medium without further consideration.[1] Inspection of Scheme 2 revealed that the reaction could be instead dedicated to the production of **3** (E–S–E′) by varying E and E′ on the same heterocyclic backbone. In that approach the target

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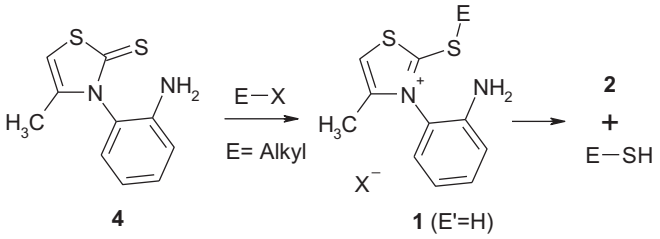
product is **3** where a sulfur atom is efficiently inserted between two electrophiles E and E′ and **2** is a by-product.

As a proof of the concept, we have already reported two series of examples in which such a metathetic process was successfully put at work.

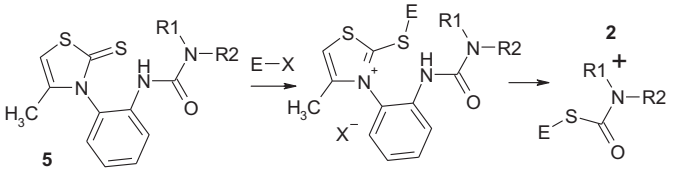
First, a series of alkylthiols was obtained in very high yields when E stands for an alkyl group and E′ is a hydrogen.[2] In that case, **1** can be considered as a latent alkylthiol, which can be quantitatively liberated under slightly basic and mild conditions. (Scheme 3) while **4** can be viewed as a masked hydrogen sulfide.



Scheme 3.

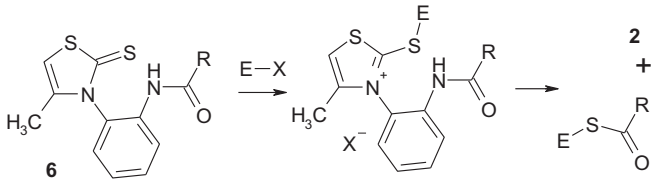
Second, a series of *S*-alkylcarbamothioates ($ESCONR_1R_2$) were quantitatively obtained when E was an alkyl group and E′ a carbamoyl group ($CONR_1R_2$).[3] Compounds **5** were prepared either from the isocyanate of **4**, which reacted with a secondary amine or reaction of **4** with an aryl or alkyl isocyanate (R_1=H).

Compounds **5** (Scheme 4) are masked stable thiocarbamic acids, which react with E–X to yield *S*-alkylcarbamothioates in high isolated yields.



Scheme 4.

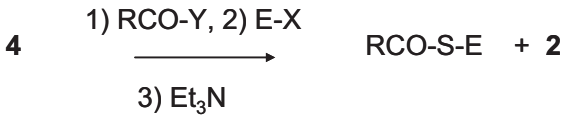
We report herein an extension of the methodology to the preparation of *S*-alkyl thioesters **3** where E is an alkyl or a benzyl group and E′ a COR group (Scheme 5).



Scheme 5.

In the approach depicted in Scheme 5, the key starting materials are rock stable heterocyclic amides **6**. They behave as masked stable thiocarboxylic acids and react with an alkyl halide to yield *S*-alkyl thioesters.

The full process starting from **4** is summarized in Scheme 6.



Scheme 6.

The acylation step leading to amide **6** shall precede the alkylation step and the sequence of these two steps cannot be interchanged. Alkylation first would lead to the salt **1** (E′=H), which immediately liberates an alkylthiol according to Scheme 3.

The unprecedented synthesis of the *S*-alkyl thioester disclosed in Scheme 6 is thus alkylthiol and thiocarboxylic acid free. The acyl group of the thioester comes from RCO–Y, the *S*-alkyl group comes from the alkylation agent E–X and the sulfur atom is provided by the thiazoline-2-thione **4**.

2. Results

2.1. Preparation of the amides 6a–e

The common starting material is *N*-(2-aminophenyl)-4-methylthiazolin-2-thione **4**, which is readily available at the multigram scale from CS_2, 1,2-diaminobenzene and 1-chloropropan-2-one.[4] Compound **4** is chemoselectively acylated at nitrogen to produce the corresponding amides **6a**–**d** in high yields. Amides **6a**,**b**,**d**, which are reported in Experimental section were obtained, in a classical way from the readily available acid chlorides [**6a** (R=Ph): PhCOCl, **6b** (R=3,5-$(CF_3)_2C_6H_3$): 3,5-$(CF_3)_2C_6H_3COCl$, **6d** (R=Cl_3C): Cl_3CCOCl]. Carboxylic acid with dicyclohexylcarbodiimide (DCC) can be employed when the corresponding acid chloride is not available. Amide **6c** (R=Me) was prepared by acetylation of **4** with stoichiometric amount of acetic anhydride catalyzed by DMAP. An excess of the acetic anhydride was found not advantageous since under basic conditions the formation of **6c** was accompanied by the formation of a by-product corresponding to a double acetylation at nitrogen. There is of course no particular novelty or difficulties in the acylation of an aniline-like compound to yield amides **6**. However stereochemical issues brought by the heterocycle in *ortho*-position of the amide group deserve some comments.

X-ray of **6a** and **6d** show that the heterocycle and the *N*-aryl group are not coplanar leading to pair of enantiomers and that the amide has an *anti* conformation in the solid state (Fig. 1). Indeed NMR analysis did not reveal the occurrence of conformers resulting from cis–trans isomerism at the amide bond for all compounds **6a**–**e**.

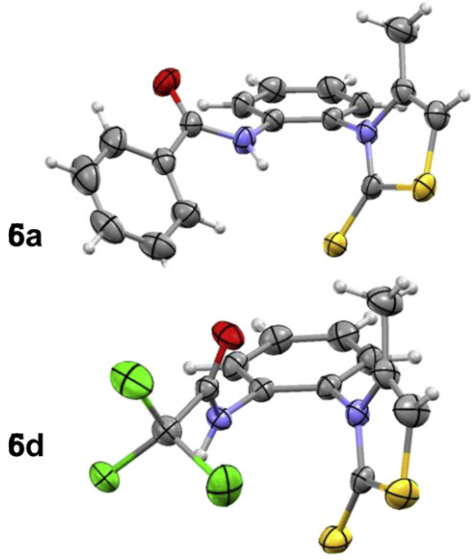
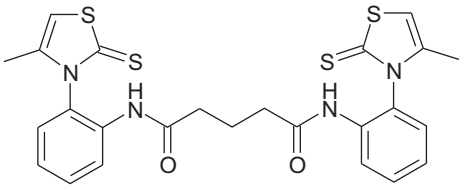


Fig. 1. X-ray of amides **6a** and **6d** (one enantiomer shown).

Compounds **6a**–**d** give rise to atropisomerism and they can be resolved into stable enantiomers on several chiral stationary phases.[5] We discovered that starting from enantiomerically pure

4,[6] the formation of the amide **6a** with benzoyl chloride led to a complete racemization while the use of DCC and benzoic acid led to the enantiomerically pure amide. This observation, which is related to the presence or the absence of acidic medium is not yet clearly understood but it is of primary importance for future extension of the metathetic process to diastereoselective acylation.



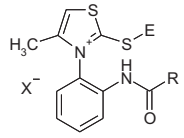
6e

Atropisomerism accounts for the splitting of most of the ^{1}H and ^{13}C signals in the diamide **6e**. In that case a mixture of diastereoisomeric compounds (*meso* and *d*,*l* forms) was obtained as confirmed by chiral HPLC on (*S*,*S*)-Whelk-O1 chiral column with online polarimetric detection (Supplementary data). Three peaks were observed. The first peak corresponds to the (+) enantiomer, the second to the *meso* form (transparent to polarimetric detection) and the third peak to the (−) enantiomer. Noteworthy, the ratio of the *meso* and *d*+*l* forms is close to 50:50, which indicates that the length of the connecting methylene chain in **6e** prevented any diastereoselective induction during the amidation steps or that equilibration took place in acidic medium. The mixture was used without any further attempts to isolate the diastereoisomers since the chirality of the samples will be lost during the last metathetic step leading to **3e**.

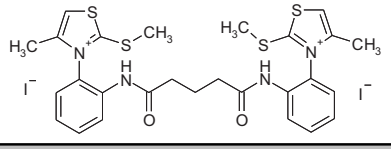
Chirality issues of the atropisomeric amides **6** are not relevant for the present study since the axial chirality will be lost during the metathetic process leading to flat thiazolobenzimidazolium **2**. Nevertheless, all these considerations on the occurrence of stable atropisomers in amides **6** and racemization during acylation of **4** contribute to a better characterization of these new compounds, which might find other applications outside the scope of the present report.

2.2. Preparation of the thiazolium salts 1

The alkylation at sulfur of *N*-substituted thiazoline-2-thiones is a well-documented second order reaction.[7] Amides **6a**–**c** and the alkylating agent smoothly yield the corresponding thiazolium salts **1a**–**e**.



1a$_1$ E=Me, R=Ph
1a$_2$ E=Et, R=Ph
1a$_3$ E=Bn, R=Ph
1b$_1$ E=Me, R= 3,5-$(CF_3)_2C_6H_3$
1b$_2$ E=Et, R= 3,5-$(CF_3)_2C_6H_3$
1b$_3$ E=Bn, R= 3,5-$(CF_3)_2C_6H_3$
1c E=$(CH_2)_2CHMe(CH_2)_2CH{=}C(Me)_2$, R=Me
1d E=Me, R=CCl_3,



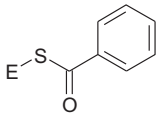
1e

In the reported examples the alkylating agents bear a halogen (bromine or iodine) but the leaving group may be, as well, a tosylate or mesylate prepared from the corresponding primary alcohol. The thiazolium salt **1d**, which resulted from the reaction of the amide **6d** with MeI was not quantitatively obtained and a part of the starting amide was recovered unchanged. X-ray of **6d** did not provide an explanation based on steric ground in the starting material. More probably strain in the thiazolium salt **1d** and the high nucleophilicity of the iodide anion accounted for the reversibility of the alkylation. Reversibility of the alkylation at sulfur is not unexpected since the charged thiazolium is an excellent leaving group. Playing with weak nucleophilic anions and (or) solvents to force the precipitation of the thiazolium salts are possible solutions to overcome the reversibility of the alkylation. Thus, the amide **6d** was quantitatively methylated using methyl tosylate without solvent at 110 °C to produce the salt **1d**. The NMR spectrum of the crude reaction mixture was particularly clean showing the sole presence of **1d**.

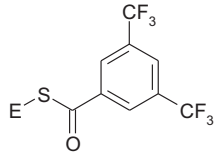
The salts **1**, when formed, were isolated in excellent yields for characterization purposes or cross-coupling experiments (see Discussion). However, in a process approach, acylation of **4**, alkylation of the resulting **6** leading to **1** and the metathetic step leading to the thioesters **3** may be sequentially performed in the same pot without isolation of the intermediates. Thiazolium salt **1b$_3$** was not isolated since the formation of the thioester **3b$_3$** already started during the alkylation step.

2.3. Preparation of thioesters 3a–e (E′=COR)

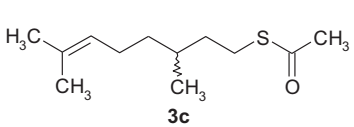
Under very mild conditions using acetonitrile as solvent and triethylamine as a base, thiazolium salts **1** undergo the metathetic process reported in Scheme 1. Equimolecular amounts of the thioester **3** and **2** are formed, they were readily separated by flash chromatography on silica gel. A washing of the reaction medium with acidified water and extraction with dichloromethane replaces advantageously the chromatography step and provide pure thioesters. The yields in isolated thioesters were particularly good. The crude reaction media did not show the formation of disulfides. More specifically, the synthetic route was exemplified by the preparation of nine thioesters **3a**–**c**,**e** from the corresponding thiazolium salts.



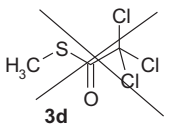
E= Me: **3a$_1$** Et: **3a$_2$** Bn: **3a$_3$**



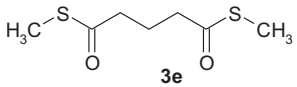
E= Me: **3b$_1$** Et: **3b$_2$** Bn: **3b$_3$**



3c



3d



3e

The thioesters **3a$_1$**, **3a$_2$**, **3b$_1$** and **3b$_2$** were prepared in excellent yields from the parent thiazolium salts. They do not convey a large molecular diversity but they were principally designed for the

cross-coupling experiments reported in the Discussion part (vide infra).

All attempts to prepare thioester **3d** from **1d** failed (vide infra).

Thiazolium salts **1** may start to spontaneously undergo the metathetic process during the alkylation step. It was observed when E (Scheme 1) was a benzyl group and E′ was −CO(3,5-$(CF_3)_2C_6H_3$). In that case a one-pot process without isolation of the intermediate thiazolium salt **1b$_3$** was used (92% isolated yield in thioester from the corresponding amide **6b**).

3. Discussion

S-Alkyl thioesters are valuable and versatile chemical intermediates.[8] Collier reviewed the different synthetic routes to these compounds in 2006.[9]

S-Alkyl thioesters can obviously be prepared according to two main routes, which are delineated by the source of sulfur atom and the bond formed in the last step.

The first group of approaches involves the reaction of an alkylthiol or a latent alkylthiol with an activated acyl group. In these two component syntheses, the alkyl–S bond is already established and the S–acyl bond is formed during the reaction. A typical example is the reaction of an alkylthiol with an acyl chloride.[10] Metal or metal-oxide catalysts like Zn, ZnO, CuO or HgO were used to activate the coupling pointing out that the metal free reaction is probably not so efficient.[11] Acid anhydrides react with alkylthiolates generated by zinc reductive cleavage of the corresponding disulfides in the presence of 10% of titanocene perfluorooctanesulfonate to yield thioesters.[12] The use of carboxylic acid as starting material requires an activation through the formation of DCC, benzotriazole or azole derivatives to allow the reaction of the thiol to proceed.[13] These activations produce stoichiometric amount of by-products in addition to the nuisance associated to the use of free alkylthiol. Tris(alkylthio)boranes as a source of latent alkylthiols have been also employed to prepare alkylthioesters from carboxylic acids.[14a] Trimethylsilyl sulfides reacted with carboxylic esters to produce thioesters.[14b]

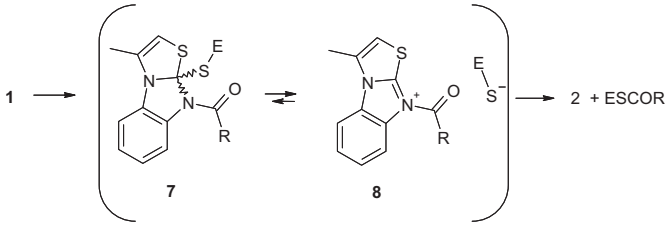
The second group of approaches deals with the reaction of thiocarboxylic acids with alkyl halides and tosylates.[15] Alcohol can be used as starting material in the presence of *i*-PrO_2CN=NCO_2*i*-Pr and PPh_3.[16] In these two component syntheses, the acyl–S bond is already established and the S–alkyl bond is formed during the reaction. Except for thioacetic and thiobenzoic acid, which are commercially available, the starting thioacid shall be prepared through acylation of hydrogen sulphide.[9,17]

A three component synthesis was recently reported by Gopinath et al. who used tetrathiomolybdate as the key sulfur transfer reagent to produce thiol esters from alcohol and carboxylic acid activated by triphenylphosphine and *N*-bromosuccinimide.[18] Good yields were obtained for primary alcohols.

In summary, most of the reported *S*-alkyl thioester syntheses involve either alkylthiols or thiocarboxylic acids as a source of sulfur. They correspond to two component syntheses with quite often the help of metal catalysts.

The amides **6a**–**e** (Scheme 5) are rock stable, crystalline and odourless compounds, which can be stored for months at room temperature. Amides **6a**–**e** can be considered as stable latent 'thiocarboxylic acids', which react with alkyl halides to yield the *S*-alkyl thioesters. From that side, the reaction we are disclosing recalls the classical formation of *S*-alkyl thioesters from thiocarboxylic acids and alkyl halides.

From another point of view, the heterocyclic part in **6a**–**e** is a latent leaving group attached to an acyl group. The leaving group will be fully activated as soon as the amide **6** is converted into the corresponding thiazolium salts **1**, which simultaneously provide a latent alkylthiol. The full expression of that outstanding activation will be encountered if the reaction mechanism goes through a -dissociation process in which an alkylthiolate is released in the medium leaving a highly activated acyl group bonded to a thiazolobenzimidazolium **8** (Scheme 7). Considered from that side, the reaction we are disclosing would recall the classical formation of *S*-alkyl thioesters from alkylthiols and activated carboxylic acids.



Scheme 7.

Intermediate **7**, which results from the direct addition of the amide nitrogen under basic conditions may lead to the formation of the thioester through a concerted intramolecular reaction. Intermediate **8**, which results from the expulsion of a thiolate from **7** is particularly hot and will also lead to the formation of the thioester. As already mentioned, intermediate **8** conveys some formal analogy with the synthesis of thioesters from activated acyl groups and alkylthiols while a process going solely through **7** conveys some formal analogy with the synthesis of thioesters from thiocarboxylic acids and alkyl halides.

One way to address these mechanistic issues was to perform cross-coupling experiments. Two salts **1** with different E and E′ groups were placed in the same flask at the same concentration in CH_3CN and treated with Et_3N at room temperature. Should the reaction proceed by an intramolecular concerted process from **7**, only two thioesters directly issuing from the parent salts shall be obtained without any cross-coupling. Should the reaction go through **8** and the medium be polar enough to allow the complete diffusion of the charge species, four thioesters shall be obtained in very similar amounts. The reactions being quantitative, a simple wash of the medium followed by a careful evaporation of the extraction solvent in vacuo allowed a quantitative NMR analysis of the resulting thioester mixture. The salts **1** were chosen in order to produce thioesters without any overlapping peak in NMR (see Supplementary data).

Salts **1a$_1$** (E=Me, E′=PhCO) and **1b$_2$** (E=Et, E′=(3,5-$(CF_3)_2C_6H_3$)CO) were chosen for a first series of cross-coupling experiments. *S*-Methyl benzenecarbothioate (**3a$_1$**) and *S*-ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_2$**) are the two thioesters directly resulting from **1a$_1$** and **1b$_2$**, respectively. They can be produced by a concerted process in the corresponding intermediates **7** or a tight ion-pair mechanism in intermediates **8**. On the other hand, *S*-ethyl benzenecarbothioate (**3a$_2$**) and *S*-ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_1$**) will definitively result from cross-coupling reactions and they will be exclusively produced through the occurrence of intermediates **8** associated with a diffusion of the thiolate ions in the medium (Scheme 8). The crude reaction medium was first checked by NMR to verify that the starting salts were quantitatively transformed. A washing of the reaction medium with acidified water and extraction with CH_2Cl_2 afforded, after drying and evaporation of the solvent, a very clean mixture of the thioesters, which was submitted to NMR analysis. (Supplementary data). The *S*-methyl benzenecarbothioate (**3a$_1$**) and *S*-ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_2$**) were obtained in the same amount and were largely dominant (82+/−1%). The thioesters resulting from the cross-coupling were indeed formed in significant amounts (18+/−1%) (Scheme 8).

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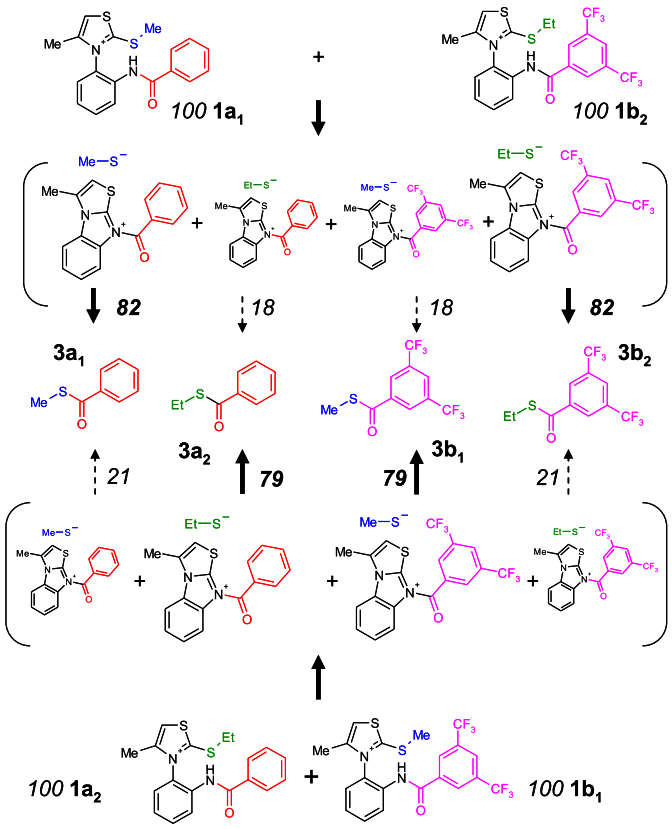

Scheme 8. Cross-coupling experiments.

These results immediately rose the point of a possible exchange between the formed thioesters in the reaction medium. The exchange between thioesters catalyzed by traces of free alkylthiols is a well-known reaction that has been exploited to produce dynamic combinatorial libraries of thioesters.[19] Are the observed cross-coupled thioesters **3a$_2$** and **3b$_1$** resulting from an on-going post-reaction exchange, which has been interrupted before the completion of a statistical distribution?

In order to address the post-reaction exchange issue, a new series of experiments were performed starting from salts **1a$_2$** (E=Et, E′=PhCO) and **1b$_1$** (E=Me, E′=(3,5-(CF$_3$)$_2$C$_6$H$_3$)CO), which were mixed in similar conditions as before for the other pair of salts. The salts **1a$_2$** and **1b$_1$** were chosen since they produce the same thioesters as the pair of salts **1a$_1$** and **1b$_2$** but now the *S*-ethyl benzenecarbothioate (**3a$_2$**) and *S*-ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_1$**) are the direct products while the *S*-methyl benzenecarbothioate (**3a$_1$**) and *S*-ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_2$**) are the products resulting from cross-coupling. Three experiments were performed at room temperature at different reaction times (5 min, 3 h and 24 h) to address the possible post-reaction interchange in the thioesters. The three experiments at different reaction times produced exactly the same ratio of thioesters and thus the occurrence of cross-coupling products is not originating from a post-reaction interchange in formed thioesters. We also learnt that the reaction is very fast since after 5 min all the salts were cleanly transformed into thioesters. Moreover, the direct products and the cross-coupling products were obtained in a similar ratio as before but of course with a memory of the starting products. The very slight difference in product partition is probably originating from a significant difference in room temperature during the two sets of experiments (Scheme 8).

All the conditions of concentration and solvent polarity being identical, it thus appears that the same contribution of the diffusion is operating from the intermediates **8**. The intermediates **8** are so hot that the possible thioester interchange and the production of disulfides are quenched.

We are in the opinion that all the formation of the thioester proceeds via the intermediate **8**, which leads to the direct thioester within a tight ion-pair while in the present experimental conditions ca. 18–21% of the ions do escape to produce cross-coupling products. A study of the concentration, temperature and polarity of the medium, which is out the scope of the paper might bring some new information.

We have already mentioned that in sharp contrast to all the successful examples, the thioester **3d** was not obtained from **1d**. Most likely, for steric and electronic reasons, the trichloroacetyl group on the nitrogen prevents the evolution towards the intermediate **7** and above all the subsequent formation of the ion-pair **8**. Products resulting from demethylation at sulfur, hydrolysis to the thiazolinone analogue of **6d** or deacylation at nitrogen leading to thiazolobenzimidazole **2** were obtained under treatment of **1d** with triethylamine under severe conditions. Under anhydrous and usual conditions employed for the metathetic transfer, the salt **1d** remained unchanged.

4. Conclusion

The synthesis of thioesters **3a**–**c**,**e** proceeded readily and in high yields through a net metathetic sulfur transfer in thiazolium salts **1**. The formation of thiazolium salts **1** resulting from the acylation at nitrogen and then the alkylation at sulfur of the readily available thiazoline-2-thione **4** are the key steps of the process. The acylation leading to stable heterocyclic amides **6** shall precede the alkylation step. The order of these two steps cannot be switched. The sulfur is brought by the heterocycle and the alkyl–sulfur bond and acyl–sulfur bond are formed in two different steps.

During the preparation of **1**, the amides **6** can be viewed as masked thiocarboxylic acids, which react with alkyl halides to produce thioesters. Cross-coupling experiments revealed that the ion-pair intermediate **8** is involved in the last step of the metathetic process from **1**. Intermediate **8** can be viewed as a highly activated acylating agent reacting with an alkylthiolate. The full process starting from amides **6** thus combines the two classical routes for the preparation of *S*-alkyl thioesters: reaction of thiocarboxylic acid on alkyl halide and reaction of alkylthiol on activated acyl agent.

It is obvious that the concomitant formation of thiazolobenzimidazole **2** is a weak point of the method. Nevertheless the reaction is particularly clean without the environmental issues associated to the use of free thiols, metal catalysts or thiocarboxylic acids.

We are currently exploring the design of **4** analogues, which can be conveniently bonded to beads.

5. Experimental section

5.1. General methods

NMR spectra were recorded at 400, 300 or 200 MHz on Bruker Avance DRX-400, DPX-300 or 200 instruments, respectively. Chemical shifts are reported in parts per million (ppm) with the signal for residual solvent as internal standard. *J* values are reported in hertz (Hz). High-resolution mass spectra were performed on a Q-STAR Elite spectrometer or on a Waters SYNAPT G2 HDMS spectrometer. Melting points were measured using a Büchi Melting Point B-545 apparatus and are not corrected. Purifications through silica gel were performed with silica gel 60 (230–400 mesh). TLC was carried out on Merck 60F$_{254}$ silica plates. The HPLC screening of chiral stationary phases was achieved on a unit composed of a Merck D-7000 system manager, a Merck-Lachrom L-7100 pump, a Merck-Lachrom L-7200

autosampler, a Merck-Lachrom L-7360 oven, a Merck-Lachrom L-7400 UV-detector and a Jasco OR-1590 polarimeter detector.

Crystallographic data for **6a** and **6d** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 909401 and CCDC 909402, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336 033; E-mail: deposit@ccdc.cam.ac.uk).

Thiazoline-thione **4** was available from previous studies,[1] or is commercially available from KaïronKem, Marseilles (info@kaironkem.com).

5.2. Synthesis of amides 6

*5.2.1. rac-N-[2-(4-Methyl-2-thioxo-1,3-thiazol-3(2H)-yl)phenyl]benzamide (**6a**).* To a solution of thiazoline-2-thione **4** (4 g, 18.0 mmol) in dichloromethane (50 mL), triethylamine (2.63 mL, 18.9 mmol) and benzoyl chloride (2.2 mL, 18.9 mmol) were added and the mixture was stirred for 48 h at room temperature. The organic layer was then washed with brine (3×75 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **6a** as a white powder (4.33 g, 74%). Mp 168 °C. R_f: 0.64 ($CHCl_3$/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.96 (d, 3H, J=1.1 Hz, CH_3), 6.36 (q, 1H, J=1.1 Hz, =CH), 7.19–7.22 (dd, 1H, J'=1.4 Hz, J''=7.9 Hz, Ar), 7.38–7.64 (m, 5H, Ar), 7.83–7.86 (m, 2H, Ar), 8.06–8.09 (dd, 1H, J'=1.2 Hz, J''=8.1 Hz, Ar), 8.36 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ=16.1, 107.5, 126.8, 127.1, 127.3 (2C), 127.7, 128.9 (2C), 130.7, 130.9, 132.2, 133.6, 134.6, 140.8, 165.7, 188.8. HRMS m/z calculated for $C_{17}H_{14}N_2OS_2$ $[M+H]^+$: 327.0620; found: 327.0620. X-ray: CCDC 909401 and Supplementary data.

*5.2.2. rac-N-[2-(4-Methyl-2-thioxo-1,3-thiazol-3(2H)-yl)phenyl]-3,5-bis(trifluoromethyl)benzamide (**6b**).* To a solution of thiazoline-2-thione **4** (4 g, 18.0 mmol) in dichloromethane (50 mL), triethylamine (2.63 mL, 18.9 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (3.42 mL, 18.9 mmol) were added and the mixture was stirred for 48 h at room temperature. The organic layer was then washed with brine (3×75 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography (petroleum ether/AcOEt, 6:4) to give **6b** as a white powder (5 g, 60%). Mp 170 °C. R_f: 0.53 (petroleum ether/AcOEt, 6:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.97 (d, 3H, J=1.0 Hz, CH_3), 6.41 (q, 1H, J=1.0 Hz, =CH), 7.22–7.25 (dd, 1H, J'=1.3 Hz, J''=7.9 Hz, Ar), 7.42–7.48 (m, 1H, Ar), 7.58–7.64 (m, 1H, Ar), 7.95–7.99 (dd, 1H, J'=1.0 Hz, J''=8.1 Hz, Ar), 8.02 (s, 1H, Ar), 8.30 (s, 2H, Ar), 8.77 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.3, 108.0, 122.8 (q, 2C, J=273.0 Hz), 125.7 (sept, 1C, J=3.8 Hz), 127.3, 127.6, 127.7 (q, 2C, J=2.7 Hz), 127.9, 131.0, 131.1, 132.5 (q, 2C, J=34.2 Hz), 133.8, 135.9, 140.8, 163.0, 188.7. HRMS m/z calculated for $C_{19}H_{12}N_2OF_6S_2$ $[M+H]^+$: 463.0368; found: 463.0363.

*5.2.3. rac-N-[2-(4-Methyl-2-thioxo-1,3-thiazol-3(2H)-yl)phenyl] acetamide (**6c**).* To a solution of thiazoline-2-thione **4** (222 mg, 1 mmol) in dichloromethane (10 mL), triethylamine (279 μL, 2 mmol), 4-dimethylaminopyridine (17 mg, 0.14 mmol) and acetic anhydride (189 μL, 2 mmol) were added and the mixture was stirred for 24 h at room temperature. The batch was diluted with dichloromethane (15 mL) and washed with water (3×20 mL), a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by chromatography (AcOEt) to give **6c** (195 mg, 74%). Mp 119 °C. R_f: 0.39 (AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.93 (d, 3H, J=1.2 Hz, CH_3), 2.06 (s, 3H, $COCH_3$), 6.38 (d, 1H, J=1.2 Hz, =CH), 7.14 (dd, 1H, J=1.2, 8.0 Hz, Ar), 7.36 (dt, 1H, J=1.2, 7.6 Hz, Ar), 7.46 (s, 1H, NH), 7.53 (dt, 1H, J=1.2, 8.0 Hz, Ar), 7.87 (d, 1H, J=8.0 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.0, 24.0, 107.2, 126.9, 127.3, 127.9, 130.7 (2C), 134.5, 140.7, 169.1, 188.9.

*5.2.4. rac-2,2,2-Trichloro-N-[2-(4-methyl-2-thioxo-1,3-thiazol-3(2H)-yl)phenyl]acetamide (**6d**).* To a solution of thiazoline-2-thione **4** (820 mg, 3.70 mmol) in dichloromethane (20 mL), triethylamine (103 μL, 0.74 mmol) and trichloracetyl chloride (453 μL, 4.07 mmol) were added at 0 °C. The mixture was stirred 10 min at 0 °C and then 20 min at room temperature. The organic layer was washed with brine (3×30 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **6d** as a white powder (1.235 g, 91%). Mp 168 °C. R_f: 0.62 ($CHCl_3$/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.96 (d, 3H, J=1.2 Hz, CH_3), 6.40 (q, 1H, J=1.2 Hz, =CH), 7.23–7.26 (dd, 1H, J'=1.5 Hz, J''=7.8 Hz, Ar), 7.49–7.54 (m, 1H, Ar), 7.61–7.67 (m, 1H, Ar), 7.82–7.85 (dd, 1H, J'=1.3 Hz, J''=8.0 Hz, Ar), 8.73 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.9, 92.3, 107.5, 127.4, 128.1, 128.6, 131.1, 132.0, 132.9, 140.2, 160.9, 189.0. HRMS m/z calculated for $C_{12}H_9Cl_3N_2OS_2$ $[M+H]^+$: 366.9295; found: 366.9298. X-ray: CCDC 909402 and Supplementary data.

*5.2.5. meso and d,l-N,N′-Bis(2-(4-methyl-2-thioxothiazol-3(2H)-yl) phenyl)glutaramide (**6e**).* To a solution of thiazoline-2-thione **4** (532 mg, 2.39 mmol) in CH_3CN (20 mL), diethylisopropylamine (425 μL, 4.88 mmol) and pentanedioyl dichloride (156 μL, 2.44 mmol) were added at room temperature. After 24 h, CH_3CN was evaporated under vacuum and $CHCl_3$ (50 mL) was added. The organic layer was washed with brine (3×50 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography (AcOEt) to give the mixture of diastereoisomers **6e** as a white powder (550 mg, 85%). Mp 98 °C. R_f: 0.25 (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.87–1.95 (m, 4H, $2CH_2$), 1.99 (d, 6H, J=1.1 Hz, $2CH_3$), 2.0 (d, 6H, J=1.1 Hz, $2CH_3$), 2.22–2.32 (m, 8H, 4 CH_2), 6.39 (q, 2H, J=1.1 Hz, 2=CH), 6.43 (q, 2H, J=1.1 Hz, 2=CH), 7.09–7.15 (m, 4H, Ar), 7.33–7.41 (m, 4H, Ar), 7.50–7.57 (m, 4H, Ar), 7.77–7.79 (m, 6H, 2Ar+4NH), 7.94–7.97 (dd, 2H, J'=0.9 Hz, J''=8.1 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.0 (2C), 16.1 (2C), 21.2, 21.5, 35.4 (4C), 107.4 (2C), 107.7 (2C), 126.7 (2C), 126.8 (2C), 127.1 (2C), 127.4 (2C), 128.0 (2C), 128.0 (2C), 130.5 (2C), 130.6 (2C), 130.7 (2C), 131.4 (2C), 134.4 (2C), 134.6 (2C), 141.0 (2C), 141.1 (2C), 171.1 (2C), 171.3 (2C), 188.6 (2C), 188.7 (2C). HRMS m/z calculated for $C_{25}H_{24}N_4O_2S_4$ $[M+H]^+$: 541.0855; found: 541.0864.

5.3. Synthesis of thiazolium salts 1

*5.3.1. rac-3-[2-(Benzoylamino)phenyl]-4-methyl-2-(methylsulfanyl)-1,3-thiazol-3-ium iodide (**1a$_1$**).* To a solution of amide **6a** (100 mg, 0.31 mmol) in CH_3CN (5 mL), iodomethane (193 μL, 3.10 mmol) was added at room temperature. After 24 h, the solvent was evaporated in vacuo and the crude product was washed with diethylether to give **1a$_1$** (135 mg, 94%). Mp 159 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.40 (s, 3H, CH_3), 2.90 (d, 3H, J=1.0 Hz, CH_3), 7.39–7.54 (m, 6H, Ar+=CH), 7.67–7.75 (m, 1H, Ar), 7.94–7.98 (m, 1H, Ar), 8.13–8.17 (m, 2H, Ar), 9.96 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.1, 19.3, 115.9, 127.0, 127.8, 128.5 (2C), 128.7 (2C), 129.3, 130.7, 132.3, 132.4, 133.0, 134.2, 147.1, 166.9, 179.5. HRMS m/z calculated for $C_{18}H_{17}N_2OS_2$ $[M-I]^+$: 341.0777; found: 341.0778.

*5.3.2. rac-3-[2-(Benzoylamino)phenyl]-2-(ethylsulfanyl)-4-methyl-1,3-thiazol-3-ium iodide (**1a$_2$**).* Amide **6a** (155 mg, 0.48 mmol) was suspended in iodoethane (1.8 mL) and the mixture was heated under reflux. After 3 h, the salt **1a$_2$** was recovered by filtration and washed with 5 mL of petroleum ether (219 mg, 96% yield). Mp 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.51 (t, 3H, J=7.4 Hz, CH_3), 2.38 (d, 3H, J=1.0 Hz, CH_3), 3.27–3.50 (m, 2H, CH_2), 7.37–7.53 (m, 6H, Ar+=CH), 7.65–7.71 (m, 1H, Ar), 7.92–7.95 (dd, 1H, J'=1.2 Hz, J''=8.1 Hz, Ar),

8.12–8.15 (m, 2H, Ar), 10.31 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.9, 15.1, 31.6, 115.8, 127.0, 127.7, 128.5 (2C), 128.7 (2C), 129.4, 130.6, 132.3, 132.4, 132.9, 134.2, 146.9, 166.8, 178.2. HRMS *m*/*z* calculated for $C_{19}H_{19}N_2OS_2$ $[M-I]^+$: 355.0933; found: 355.0922.

*5.3.3. rac-3-[2-(Benzoylamino)phenyl]-2-(benzylsulfanyl)-4-methyl-1,3-thiazol-3-ium bromide (**1a$_3$**).* Amide **6a** (70 mg, 0.21 mmol) was suspended in benzylbromide (1 mL) and the mixture was heated under reflux. After 1 h, the salt **1a$_3$** was recovered by filtration and washed with 5 mL of petroleum ether (91 mg, 86% yield). Mp 162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.31 (d, 3H, *J*=0.9 Hz, CH_3), 4.56 (d, 1H, J_{A-B}=12.3 Hz, CH_A), 4.77 (d, 1H, J_{A-B}=12.3 Hz, CH_B), 7.28–7.53 (m, 11H, Ar+=CH), 7.65–7.70 (m, 1H, Ar), 7.97–8.00 (dd, 1H, *J*′=1.1 Hz, *J*″=8.1 Hz, Ar), 8.24–8.26 (m, 2H, Ar), 10.77 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.7, 41.3, 116.6, 126.7, 127.4, 128.4 (2C), 129.0 (2C), 129.0 (2C), 129.2 (2C), 129.5 (2C), 131.2, 131.8, 132.2, 132.5, 132.7, 134.5, 146.1, 167.3, 177.6. HRMS *m*/*z* calculated for $C_{24}H_{21}N_2OS_2$ $[M-Br]^+$: 417.1090; found: 417.1094.

*5.3.4. rac-3-(2-{[3,5-Bis(trifluoromethyl)benzoyl]amino}phenyl)-2-(methylsulfanyl)-4-methyl-1,3-thiazol-3-ium iodide (**1b$_1$**).* To a solution of amide **6b** (100 mg, 0.22 mol) in CH_3CN (5 mL), iodomethane (137 μL, 2.20 mmol) was added at room temperature. After 24 h, the solvent was evaporated in vacuo to give **1b$_1$** (117 mg, 90%). Mp 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.40 (d, 3H, *J*=1.0 Hz, CH_3), 2.88 (s, 3H, CH_3), 7.44–7.58 (m, 2H, Ar), 7.65–7.73 (m, 2H, Ar+=CH), 7.94–7.98 (m, 2H, Ar), 8.61 (s, 2H, Ar), 10.77 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.1, 19.0, 117.1, 122.9 (q, 2C, *J*=273.0 Hz), 125.7 (sept, 1C, *J*=3.6 Hz), 127.3, 128.4, 129.3 (q, 2C, *J*=2.8 Hz), 129.6, 130.5, 131.7 (q, 2C, *J*=33.9 Hz), 132.9, 133.3, 134.5, 146.7, 164.2, 178.9. HRMS *m*/*z* calculated for $C_{20}H_{15}N_2OF_6S_2$ $[M-I]^+$: 477.0525; found: 477.0523.

*5.3.5. rac-3-(2-{[3,5-Bis(trifluoromethyl)benzoyl]amino}phenyl)-2-(ethylsulfanyl)-4-methyl-1,3-thiazol-3-ium iodide (**1b$_2$**).* Amide **6b** (100 mg, 0.22 mmol) was suspended in iodoethane (2 mL) and the mixture was heated under reflux. After 24 h, dichloromethane (2 mL) was added and the mixture was filtered through a pad of silica gel under vacuum. The silica was washed with dichloromethane to eliminate unreacted iodoethane and then with methanol to collect the thiazolium salt. The methanol was then evaporated in vacuo to yield **1b$_2$** (115 mg, 86% yield). Mp 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.54 (t, 3H, *J*=7.4 Hz, CH_3), 2.43(d, 3H, *J*=0.9 Hz, CH_3), 3.29–3.51 (m, 2H, CH_2), 7.42–7.45 (dd, 1H, *J*′=1.2 Hz, *J*″=8.0 Hz, Ar), 7.53–7.59 (m, 2H, Ar+=CH), 7.69–7.75 (m, 1H, Ar), 7.96–8.00 (m, 2H, Ar), 8.60 (s, 2H, Ar), 10.67 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.8, 15.3, 31.5, 116.5, 122.9 (q, 2C, *J*=273.0 Hz), 125.6–125.9 (sept, 1C, *J*=3.5 Hz), 127.2, 128.5, 129.4 (q, 2C, *J*=3.0 Hz), 129.7, 130.6, 131.7 (q, 2C, *J*=34.0 Hz), 133.0, 133.2, 134.6, 146.6, 164.3, 177.8. HRMS *m*/*z* calculated for $C_{21}H_{17}N_2OF_6S_2$ $[M-I]^+$: 491.0681; found: 491.0670.

*5.3.6. 3-[2-(Acetylamino)phenyl]-2-[(3,7-dimethyloct-6-en-1-yl)sulfanyl]-4-methyl-1,3-thiazol-3-ium iodide (**1c**).* To a solution of amide **6c** (69 mg, 0.26 mmol) in chloroform (2 mL), citronellyl iodide (439 mg, 1.65 mmol)[20] was added and the mixture was heated under reflux. After 24 h, dichloromethane (10 mL) was added and the mixture was filtered through a pad of silica gel under vacuum. The silica was washed with dichloromethane, then with ethylacetate and finally with methanol to collect the thiazolium salt. The methanol was then evaporated in vacuo to yield **1c** (79 mg, 57%). Mp 67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (dd, 3H, *J*=3.6, 10.0 Hz, CH_3), 1.07–1.21 (m, 2H, CH_2), 1.23–1.38 (m, 1H, CH), 1.54 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.70–2.05 (m, 4H, $2CH_2$), 2.32 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.20–3.38, 3.48–3.65 (m, 2H, SCH_2), 5.00 (tt, 1H, *J*=1.2, 6.8 Hz, =CH), 7.20–7.96 (m, 5H, Ar+C=CH), 9.55 (d, 1H, *J*=2.4 Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7, 17.6, 18.9, 24.6, 25.1, 25.6, 31.9, 34.2, 35.3, 36.4, 111.9, 117.2, 123.9, 126.0, 127.3, 129.1, 131.6, 132.7, 134.0, 145.8, 170.6, 178.6. HRMS *m*/*z* calculated for $C_{22}H_{31}N_2OS_2$ $[M-I]^+$: 403.6238; found: 403.6240.

*5.3.7. rac-3-[2-(2,2,2-Trichloroacetamido)phenyl]-2-(methylsulfanyl)-4-methyl-1,3-thiazol-3-ium paratoluenesulfonate (**1d**).* To a solution of amide **6d** (802 mg, 2.19 mmol) in CH_3CN (4 mL), methyl tosylate (407 mg, 2.19 mmol) was added and the mixture was heated under reflux. After 3 h, the solvent was evaporated and the crude product was dried in vacuo to give **1d** (1.148 g, 95%) as a brown powder. Mp 96 °C. ^{1}H NMR (400 MHz, CD_3CN): δ=2.31 (d, 3H, *J*=1.1 Hz, CH_3), 2.36 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.16 (d, 2H, *J*=7.9 Hz, Ar), 7.60 (d, 2H, *J*=7.9 Hz, Ar), 7.63–7.66 (m, 2H, Ar), 7.70–7.76 (m, 2H, Ar), 7.81–7.87 (m, 1H, Ar), 9.85 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.8, 18.9, 21.3, 117.4, 126.8 (2C), 129.2 (2C), 129.3, 130.8, 130.9, 131.3 (2C), 133.1, 134.1, 139.7 (2C), 148.3, 162.3, 181.0. HRMS *m*/*z* calculated for $C_{13}H_{12}N_2OS_2Cl_3$ $[M-TsO^-]^+$: 380.9451; found: 380.9449.

*5.3.8. 3,3′-[(1,5-Dioxopentane-1,5-diyl)bis(iminobenzene-2,1-diyl)]bis[4-methyl-2-(methylsulfanyl)-1,3-thiazol-3-ium]diiodide (**1e**).* To a solution of diamide **6e** (112 mg, 0.21 mmol) in CH_3CN (5 mL), iodomethane (258 μL, 4.14 mmol) was added at room temperature. After 24 h, the solvent was evaporated in vacuo and the crude product was washed with CH_3CN (5 mL) to give **1e** (140 mg, 82%) as a white powder. Mp 168 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.56–1.65 (m, 2H, $2CH_2$), 2.18–2.25 (d+m, 10H, $2CH_3$+$2CH_2$), 2.91 (s, 6H, 4 CH_3), 7.48–7.54 (m, 2H, Ar), 7.64–7.77 (m, 6H, Ar), 7.96 (q, 2H, *J*=1.1 Hz, 4=CH), 9.83 (s, 2H, 4NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ=13.8 (2C), 17.7 (2C), 21.0 (1C), 34.6 (2C), 117.2 (2C), 126.9 (2C), 127.0 (2C), 127.4 (2C), 128.0 (2C), 132.4 (2C), 133.7 (2C), 146.0 (2C), 171.1 (2C), 178.8 (2C). HRMS *m*/*z* calculated for $C_{27}H_{30}N_4O_2S_4$ $[M-2I]^{2+}$: 285.0620; found: 285.0625.

5.4. Synthesis of thioesters 3

5.4.1. Synthesis from thiazolium salts

*5.4.1.1. S-Methyl benzenecarbothioate (**3a$_1$**).*[21] A solution of thiazolium salt **1a$_1$** (98 mg, 0.21 mmol) and triethylamine (29 μL, 0.21 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3a$_1$** (28 mg, 88%) as a pale yellow oil. R_f: 0.76 ($CHCl_3$/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.48 (s, 3H, CH_3), 7.43–7.60 (m, 3H, Ar), 7.95–7.98 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.7, 127.1 (2C), 128.6 (2C), 133.3, 137.1, 192.5. HRMS *m*/*z* calculated for C_8H_8OS $[M+H]^+$: 153.0369; found: 153.0368.

*5.4.1.2. S-Ethyl benzenecarbothioate (**3a$_2$**).*[21a] A solution of thiazolium salt **1a$_2$** (106 mg, 0.22 mmol) and triethylamine (31 μL, 0.22 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3a$_2$** (34 mg, 93%) as a pale yellow oil. R_f: 0.77 ($CHCl_3$/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.36 (t, 3H, *J*=7.4 Hz, CH_3), 3.08 (q, 2H, *J*=7.4 Hz, CH_2), 7.42–7.59 (m, 3H, Ar), 7.95–7.98 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.8, 23.4, 127.1 (2C), 128.6 (2C), 133.2, 137.2, 192.1. HRMS *m*/*z* calculated for $C_9H_{10}OS$ $[M+H]^+$: 167.0525; found: 167.0522.

*5.4.1.3. S-Benzyl benzenecarbothioate (**3a$_3$**).*[22] A solution of thiazolium salt **1a$_3$** (61 mg, 0.12 mmol) and triethylamine (17 μL, 0.12 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3a$_3$**

(25 mg, 90%) as a pale yellow oil. R_f: 0.75 ($CHCl_3$/AcOEt, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ=4.33 (s, 2H, CH_2), 7.25–7.48 (m, 7H, Ar), 7.54–7.60 (m, 1H, Ar), 7.96–7.99 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=33.3, 127.3 (2C), 127.3, 128.6 (2C), 128.6 (2C), 129.0 (2C), 133.4, 136.8, 137.5, 191.3. HRMS m/z calculated for $C_{14}H_{12}OS$ $[M+H]^+$: 229.0682; found: 229.0680.

*5.4.1.4. S-Methyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_1$**).* A solution of thiazolium salt **1b$_1$** (106 mg, 0.22 mmol) and triethylamine (31 μL, 0.22 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3b$_1$** (30 mg, 83%) as a pale yellow oil. R_f: 0.76 ($CHCl_3$/AcOEt 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ=2.56 (s, 3H, CH_3), 8.07 (s, 1H, Ar), 8.39 (s, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.0, 122.8 (q, 2C, J=273.0 Hz), 126.3–126.5 (sept, 1H, J=3.5 Hz), 127.2 (q, 2C, J=3.2 Hz), 132.4 (q, 2C, J=34.2 Hz), 138.6, 189.9. HMRS: ionization of the sample under various conditions failed.

*5.4.1.5. S-Ethyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_2$**).* A solution of thiazolium salt **1b$_2$** (116 mg, 0.19 mmol) and triethylamine (26 μL, 0.19 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3b$_2$** (52.5 mg, 93%) as a pale yellow oil. R_f: 0.8 ($CHCl_3$/AcOEt 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.39 (t, 3H, J=7.4 Hz, CH_3), 3.16 (q, 2H, J=7.4 Hz, CH_2), 8.06 (s, 1H, Ar), 8.38 (s, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.5, 24.1, 122.8 (q, 2C, J=273 Hz), 126.2–126.4 (sept, 1H, J=3.6 Hz), 127.2 (q, 2C, J=3.2 Hz), 132.4 (q, 2C, J=34.1 Hz), 138.8, 189.6. HRMS m/z calculated for $C_{11}H_8OSF_6$ $[M+Ag]^+$: 408.9246; found: 408.9247.

*5.4.1.6. rac-S-3,7-Dimethyloct-6-en-1-yl ethanethioate (**3c**).*[23] A solution of thiazolium salt **1c** (190 mg, 0.47 mmol) and triethylamine (66 μL, 0.47 mmol) in acetonitrile (5 mL) was stirred at room temperature for 3 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography (CH_2Cl_2) to give **3c** (64 mg, 64%) as a yellow oil. R_f: 0.76 (CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ=0.90 (d, 3H, J=6.4 Hz, CH_3), 1.11–1.21 (m, 1H, CH), 1.27–1.62 (m, 4H, $2CH_2$), 1.60 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.90–2.05 (m, 2H, CH_2), 2.32 (s, 3H, $COCH_3$), 2.83–2.98 (m, 2H, SCH_2), 5.08 (tt, 1H, J=1.2, 7.0 Hz, =CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.6, 19.1, 25.4, 25.7, 27.0, 30.6, 32.0, 36.5, 36.7, 124.6, 131.3, 196.0. HRMS m/z calculated for $C_{12}H_{22}OS$ $[M+H]^+$: 215.1464; found: 215.1466.

*5.4.1.7. S^1,S^5-Dimethyl pentanebis(thioate) (**3e**).* A solution of thiazolium salt **1e** (117 mg, 0.21 mmol) and triethylamine (58 μL, 0.42 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$) to give **3e** (24 mg, 88%) as an oil. R_f: 0.54 ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ=2.03 (quint, 2H, CH_2), 2.30 (s, 6H, $2CH_3$), 2.62 (t, 4H, J=7.3 Hz, $2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ=11.6 (2C), 21.3, 42.5 (2C), 198.9 (2C). HRMS m/z calculated for $C_7H_{12}O_2S_2$ $[M+Na]^+$: 215.0171; found: 215.0171.

*5.4.2. One-pot synthesis of S-benzyl 3,5-bis(trifluoromethyl)benzenecarbothioate (**3b$_3$**) without isolation of the thiazolium salt **1b$_3$**.* A solution of amide **6b** (80 mg, 0.17 mmol) and benzylbromide (20 μL, 0.17 mmol) in acetonitrile (5 mL) was refluxed for 24 h. After cooling, triethylamine (24 μL) was added and the solution stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the crude product was purified by chromatography ($CHCl_3$/AcOEt, 9:1) to give **3b$_3$** (57 mg, 92%) as a pale yellow oil. R_f: 0.75 ($CHCl_3$/AcOEt, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ=4.39 (s, 2H, CH_2), 7.28–7.40 (m, 5H, Ar), 8.06 (s, 1H, Ar), 8.39 (s, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=33.9, 122.7 (q, 2C, J=273.0 Hz), 126.5–126.6 (sept, 1H, J=3.6 Hz), 127.3 (q, 2C, J=3.2 Hz), 127.8, 128.8 (2C), 129.0 (2C), 132.4 (q, 2C, J=34.2 Hz), 136.4, 138.4, 188.9. HRMS m/z calculated for $C_{16}H_{10}OSF_6$ $[M+I]^-$: 490.9407; found: 490.9411.

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Supplementary data

X-ray data for **6a** and **6d**, ^1H and ^{13}C NMR spectra of the compounds. HPLC on chiral support of **6e**. ^1H NMR of cross-coupling experiments. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.013.

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