Tetrahedron 66 (2010) 1852–1858

Contents lists available at ScienceDirect

Tetrahedron

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

Metathetic sulfur transfer mediated by *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione derivatives: a route to diversely substituted *S*-alkylcarbamothioates

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ARTICLE INFO

Article history:
Received 3 December 2009
Received in revised form 30 December 2009
Accepted 5 January 2010
Available online 11 January 2010

Keywords:
Sulfur transfer
Heterocycle
Thiazolin-2-thione
Alkylation
Urea

ABSTRACT

A new route to *S*-alkylcarbamothioates is disclosed. In a first step, *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione is transformed into a mono- or disubstituted urea at nitrogen, and then in a second step, alkylated at sulfur. The resulting salts, after treatment with a base, gave *S*-alkylcarbamothioates in high isolated yields together with 3-methyl[1,3]thiazolo[3,2-*a*]benzimidazole under very mild conditions.

1. Introduction

Compound **1a** was designed to perform enantioselective extraction of carboxylates of *N*-protected amino acids (Fig. 1).

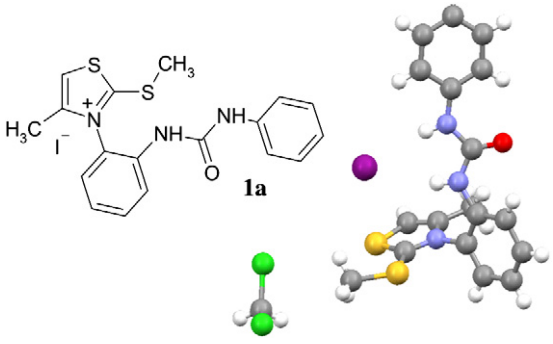
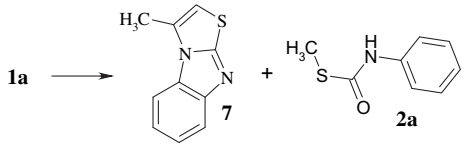


Figure 1. 4-Methyl-2-(methylthio)-3-(2-(3-phenylureido)phenyl)thiazol-3-ium iodide (**1a**). X-ray of **1a** including a CH_2Cl_2 molecule, iodine-violet, chlorine-green, nitrogen-blue, oxygen-red, sulfur-yellow.

Compound **1a** conveys the appropriate molecular characteristics to achieve this goal: an axial chirality, a urea in a suitable conformation for double hydrogen bonding with a carboxylate anion and a positive charge to enhance the binding through electrostatic interaction. X-ray of **1a** showed that the iodide anion developed simultaneous H-bonding with the two parallel NH of the urea; it was an encouraging hint to introduce **1a** in the very active field of anion selective receptors.[1,2] To our surprise, **1a** in the presence of a carboxylate anion, which acted as a base, was readily and quantitatively transformed into 3-methyl[1,3]thiazolo[3,2-a]benzimidazole **7**, which was known from a previous study,[3] and *S*-methyl phenylcarbamothioate **2a** (Scheme 1). The reaction was particularly clean and proceeded at room temperature in CD_3CN during NMR analysis.



Scheme 1. Metathetic process leading to **7** and carbamothioate **2a** from **1a**.

The outcome of the new reaction depicted in Scheme 1 corresponds to a metathetic process in which a carbamothioate framework is obtained by connecting two molecular fragments bound to a heterocyclic template, which concomitantly gives the highly conjugated heterocycle **7**.

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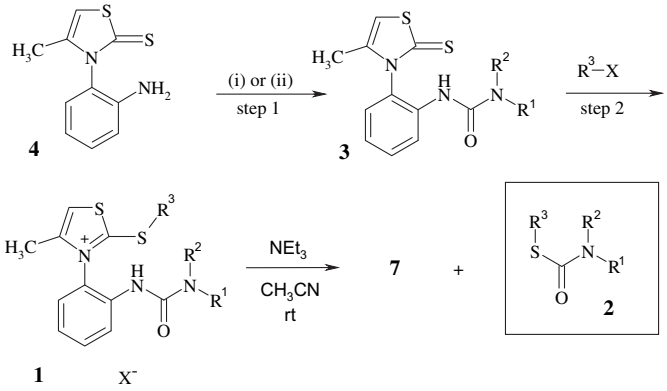
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.020

S-Alkyl alkylcarbamothioates, *S*-alkyl dialkylcarbamothioates and *S*-alkyl arylcarbamothioates constitute a highly valuable class of compounds since they are active on diverse biological targets. Synthesis and properties of carbamothioates have been recently reviewed in 2005 by Rossi.[4] *S*-alkylcarbamothioates such as Molinate, Ethiolate or EPTC are produced at the multi-ton scale as agrochemicals. Obviously, the reaction described in Scheme 1 cannot be used for a large scale preparation of *S*-alkylcarbamothioates since for each mole of **2a**, a mole of **7** is produced in a very poor atom economy. Nevertheless, we believe that there is room for a safe, clean and flexible method to prepare libraries of very pure *S*-alkylcarbamothioates for screening purposes. The main concern in the previously reported synthesis of *S*-alkylcarbamothioates is the occurrence of several sulfur containing by-products generated by the sulfur source (S_8,[5] COS,[6] thioureas,[7] thiocyanates,[8] alkylmercaptans,[6,9] alkyldisulfides,[10] LiAlHSH[11]). These by-products and the *S*-alkyl carbamothioate are formed during the same reaction step and the isolation of the targeted compound requires extensive purification. As said before the reaction described in Scheme 1 is very efficient in term of sulfur atom: one of the sulfur atoms is quantitatively transferred and the second sulfur atom is trapped into an aromatic structure. Results using the unprecedented methodology described in Scheme 1 are reported herein.

2. Results and discussion

Large libraries of thiazolium salts **1** can be selectively prepared in high yield from urea derivatives **3** by alkylation at sulfur (Scheme 2). Alkylation at sulfur in *N*-substituted thiazoline-2-thiones is a well documented bimolecular reaction which can be performed with various alkylating agents such as alkyltosylates or alkyl halides in polar aprotic solvents.[12] Alkyl iodides were chosen to exemplify the reaction. The consumption of **3** was monitored by TLC. Salts **1a–n** were obtained in isolated yields greater than 96% from the corresponding ureas **3a–n**.



(i) R^1-N=C=O (R^2= H); (ii) triphosgene, R^1NHR^2

Scheme 2. Two steps synthesis of **1a–n** from *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4**.

Thiazolium salts **1a–n** in the presence of a base such as triethylamine in CH_3CN were transformed in less than 15 min in carbamothioates **2a–n** and 3-methyl[1,3]thiazolo[3,2-*a*]benzimidazole **7** at room temperature. In all the reported examples the reaction media were outstandingly clean. The substituent diversity on the nitrogen is brought by the substituent(s) of the starting urea formed in Step 1, while the substituent diversity at sulfur in carbamothioates **2** is brought by the alkylating agent (R^3-X) in Step 2. Selected examples are reported in Table 1. The isolated yields in **2a–n** from **3a–n** were greater than 90% for two combined steps (Scheme 2). Diversely substituted ureas **3a–n** were obtained by reacting the amino group of *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4** with a series of commercially available isocyanates (procedure A, Table 1) or by a triphosgene mediated coupling of the amino group of **4** with the corresponding primary or secondary amines (procedure B, Table 1). Ureas **3l–n** were prepared to illustrate the preparation of the well known Molinate, Ethiolate and EPTC, respectively.

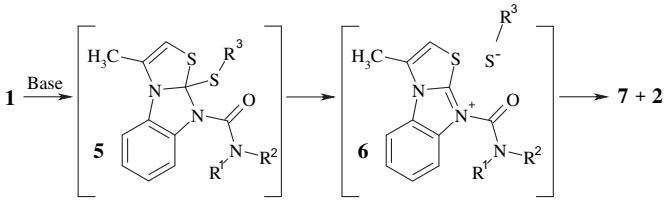
Table 1
Isolated yields in carbamothioates **2** from compounds **1** (Y/**1**), compounds **2** (Y/**2**) and *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4** (Y/**4**)

Cpd	R^1	R^2	R^3	[a]	Y/1	Y/3	Y/4
2a	Phenyl	H	Me	A	95	92	86
2b	*p*-Tolyl	H	Me	A	94	91	87
2c	3,5-Bis TFMP[b]	H	Me	A	93	90	87
2d	4-Nitrophenyl	H	Me	A	96	94	91
2e	3,5-Bis TFMB[c]	H	Me	B	96	95	60
2f	Phenyl	H	Et	A	93	91	85
2g	*p*-Tolyl	H	Et	A	96	90	87
2h	3,5-Bis TFMB[c]	H	Et	B	94	90	57
2i	*i*-Pr	H	Et	B	97	96	72
2j	Phenyl	H	Decyl	A	97	93	87
2k	*p*-Tolyl	H	Decyl	A	95	92	88
2l[d]	$-(CH_2)_6-$		Et	B	—[g]	95	64
2m[e]	Et	Et	Et	B	—[g]	96	66
2n[f]	Pr	Pr	Et	B	—[g]	96	61

[a] Urea route: A: R^1NCO, CH_3CN; B: Triphosgene, NEt_3, CH_2Cl_2 then R^1R^2NH.
[b] Bis TFMP=3,5-bis(trifluoromethyl)phenyl.
[c] bis TFMB=3,5-bis(trifluoromethyl)benzyl.
[d] Molinate.
[e] Ethiolate.
[f] EPTC.
[g] Thiazolium salts have not been isolated.

The key starting material *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4** is readily available at a multigram scale from CS_2, 1,2-diaminobenzene and 1-chloro-propan-2-one.[13] It is worth mentioning that all the by-product issues linked to the sulfur source in classical carbamothioate syntheses are solved once and for all during the preparation of **4** with no significant incidence on the purity of **2**, two steps later.

Under basic conditions, the mechanism of the metathetic reaction leading to **2** from **1** probably involves the formation of a neutral tetrahedral intermediate **5** by addition of the nitrogen of the urea to the highly activated C-2 carbon in the thiazolium salt **1** (Scheme 3). The stable conformation observed by X-ray for **1a** reveals that the nitrogen of the urea is situated in a plane perpendicular to the heterocyclic framework, in an ideal situation for a nucleophilic addition at the electrophilic C-2 position. The best leaving group in the resulting tetrahedral intermediate **5** is obviously the R^3S^- group, which further attacks the highly activated intermediate **6** to yield the final products.



Scheme 3. Proposed intermediates to obtain carbamothioates **2a–n** from thiazolium salts **1a–n**.

The proposed intermediate **6** is so highly activated that one may envision a concerted process within a tight ion pair consisting of R^3S^- and **6**. In order to address this issue experiments were performed in which equimolecular amounts of the two salts **1k** (R^1=*p*-tolyl, R^3=*n*-decyl) and **1a** (R^1=phenyl, R^3=methyl) were mixed and simultaneously treated with triethylamine in methanol. The crude

reaction mixture was analysed by ESI-MS after evaporation of the solvent. Compounds with masses (M+1 and M+Na) corresponding to the four possible *S*-alkylcarbamothioates **2** were obtained in similar amount. Thus, the two expected *S*-alkylcarbamothioates **2k** (R^1=*p*-tolyl, R^3=*n*-decyl) and **2a** (R^1=phenyl, R^3=methyl) resulting from the parent salts **1k** and **1a** and the two *S*-alkylcarbamothioates resulting from cross-coupling **2b** (R^1=*p*-tolyl, R^3=methyl) and **2j** (R^1=phenyl, R^3=*n*-decyl) were obtained. These experiments ruled out any tight ion pair intramolecular mechanism in the formation of the *S*-alkylthiocarbamates **2**. They also ruled out the formation of **7** and **2** from a concerted elimination occurring in **5**.

3. Conclusion

In summary carbamothioates **2** are prepared in high yield from thiazolium salts **1**, which are obtained in a two-step process from *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4** acting as a clean sulfur transfer agent. In the present study, 3-methyl[1,3]-thiazolo[3,2-*a*]benzimidazole **7** is a signature of the starting heterocycle **4**. Obviously changed signatures would be obtained starting from other frameworks presenting a thiocarbonyl group and an aminophenyl group in a topological relationship similar to the one encountered in **4**. The design of analogues of *N*-(2-aminophenyl)-4-methyl-thiazolin-2-thione **4**, which can be conveniently attached to a Merrifield bead is underway to provide a traceless solid-phase synthesis of *S*-alkylcarbamothioates **2**.

4. Experimental section

4.1. General information

^{1}H NMR spectra were recorded at 500, 400, 300 or 200 MHz and ^{13}C NMR spectra at 125, 100, 75 or 50 MHz on Bruker Avance DRX-500 or 400, DPX-300 or 200 instruments, respectively. Chemical shifts are reported in ppm with the signal for residual solvent as internal standard. *J* values are reported in Hertz. High resolution mass spectra were performed on Q-STAR Elite spectrometer. Melting points were measured using a Büchi Melting Point B-545 apparatus or a Kofler hot stage apparatus and are not corrected. Filtrations through silica gel were performed with silica gel 60 (230–400 mesh). TLCs were carried out on Merck 60F_{254} silica plates.

Crystallographic data for **1a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC-756573. This 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:044(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

4.2. General procedure (A) for the preparation of ureas 3a–d

Compound **4** (1 g, 4.5 mmol) is solubilised in CH_3CN (10 mL). Then the corresponding isocyanate (1.05 equiv) was added and the solution stirred at room temperature. After 24 h the solvent was removed and the resulting solid recrystallized from CH_2Cl_2.

*4.2.1. 1-(2-(4-Methyl-2-thioxothiazol-3(2H)-yl)phenyl)-3-phenylurea (**3a**).* Compound **3a** was available from a previous study.[2]

*4.2.2. 1-(2-(4-Methyl-2-thioxothiazol-3(2H)-yl)phenyl)-3-p-tolylurea (**3b**).* Yield: 96% (1.55 g, colourless crystals); mp 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (d, 3H, *J*=1.1 Hz; CH_3), 2.23 (s, 3H; CH_3), 6.93 (q, 1H, *J*=1.1 Hz; H5), 7.06–7.31 (m, 6H; Ar), 7.44–7.50 (m, 1H; Ar), 7.66 (s, 1H; NH), 8.11–8.14 (m, 1H; Ar), 9.07 (s, 1H; NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.95, 20.32, 107.85, 118.23 (2C), 122.63, 123.55, 127.50, 129.08, 129.25 (2C), 129.96, 130.90, 135.96, 136.76, 140.00, 152.28, 189.18; HRMS *m*/*z* calcd $C_{18}H_{18}N_3OS_2$ $[M+H]^+$: 356.0886; found: 356.0883.

*4.2.3. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(4-methyl-2-thioxothiazol-3(2H)-yl)phenyl)urea (**3c**).* Yield: 97% (2.08 g, colourless crystals); mp 221–223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (d, 3H, *J*=0.8 Hz; CH_3), 6.65 (q, 1H, *J*=0.8 Hz; H5), 6.84–6.93 (m, 6H; Ar), 7.13–7.19 (m, 1H; Ar), 7.20–7.28 (m, 1H; Ar), 7.34 (s, 1H; NH), 7.46 (s, 1H; Ar), 7.72 (s, 2H; Ar), 8.11–8.19 (m, 1H; Ar), 8.31 (s, 1H; NH); ^{13}C NMR (75 MHz, CDCl3) δ 15.31, 110.12, 115.52(sept, 2C; *J*=4 Hz), 118.07 (q, 2C; *J*=3 Hz), 123.20 (q, 2C; *J*=273 Hz), 123.53, 124.82, 126.94, 128.35, 131.29, 131.79 (q, 2C; *J*=33 Hz), 135.38, 140.31, 141.42, 151.40, 189.87; $C_{19}H_{13}F_6N_3OS_2$ requires: C, 47.80; H, 2.74; N, 8.80; S, 13.43. Found: C, 47.70; H, 2.46; N, 8.76; S, 13.32.

*4.2.4. 1-(2-(4-Methyl-2-thioxothiazol-3(2H)-yl)phenyl)-3-(4-nitrophenyl)urea (**3d**).* Yield: 97% (1.69 g, yellow crystals); mp 249–251 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.85 (d, 3H, *J*=1.1 Hz; CH_3), 6.94 (q, 1H, *J*=1.1 Hz; H5), 7.20–7.34 (m, 2H; Ar), 7.45–7.55 (m, 1H; Ar), 7.58–7.70 (m, 2H; Ar), 7.93 (s, 1H; NH), 8.02–8.12 (m, 1H; Ar), 8.13–8.25 (m, 2H; Ar), 9.83 (s, 1H; NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.00, 107.95, 117.54 (2C), 123.48, 124.64, 125.20 (2C), 128.40, 129.20, 130.12, 135.12, 139.98, 141.22, 145.90, 151.92, 189.11; HRMS *m*/*z* calcd $C_{17}H_{14}N_4O_3S_2$ $[M+H]^+$: 387.0580; found: 387.0579.

4.3. General procedure (B) for the preparation of ureas 3e–i

A solution of **4** (300 mg, 1.35 mmol) and NEt_3 (2 equiv, 2.70 mmol) in dry CH_2Cl_2 (10 mL) is added dropwise to a solution of triphosgene (1 equiv, 0.45 mmol) in dry CH_2Cl_2 (5 mL). The solution is stirred for 1 h at room temperature and then the corresponding amine (1.1 equiv) is added. After 12 h dry CH_2Cl_2 is added and the solution washed 3×25 mL of brine. The organic layer is dried over $MgSO_4$ and evaporated to dryness. The resulting solid is purified by silica gel chromatography.

*4.3.1. 1-(3,5-Bis(trifluoromethyl)benzyl)-3-(2-(4-methyl-2-thioxothiazol-3(2H)-yl)phenyl)urea **3e**.* Yield: 62% (411 mg, white solid); mp 167–169 °C; R_f=0.50 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.81 (d, 3H, *J*=1.2 Hz; CH_3), 4.35–4.55 (m, 2H; CH_2), 6.87 (q, 1H, *J*=1.2 Hz; H5), 7.12–7.20 (m, 2H; Ar), 7.36–7.47 (m, 3H; Ar and NH), 7.71 (s, 1H; NH), 7.94 (s, 2H; Ar), 7.98 (s, 1H; Ar), 8.03–8.09 (m, 1H; Ar); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.80, 41.93, 107.64, 120.53 (sept, 1C, *J*=4 Hz), 122.48, 123.21, 123.37 (q, 2C, *J*=273 Hz), 127.25, 127.82 (q, 2C, *J*=3 Hz), 129.03, 129.88, 130.17 (q, 2C, *J*=33 Hz), 136.34, 139.94, 144.06, 155.15, 189.17; HRMS *m*/*z* calcd $C_{20}H_{16}F_6N_3OS_2$ $[M+H]^+$: 492.0634; found: 492.0639.

*4.3.2. 1-Isopropyl-3-(2-(4-methyl-2-thioxothiazol-3(2H)-yl)phenyl) urea (**3f**).* Yield: 75% (311 mg, white solid); mp 198–200 °C; R_f=0.36 (CH_2Cl_2/AcOEt, 7.5/2.5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (d, 3H, J_1=6.5 Hz; CH_3), 1.08 (d, 3H, J_1=6.5 Hz; CH_3), 1.81 (d, 3H, *J*=1.2 Hz; CH_3), 3.60–3.78 (sept, d, 1H, J_1=6.5 Hz, J_2=7.0 Hz; CH), 6.72 (d, 1H, J_2=7.0; NH), 6.90 (q, 1H, *J*=1.2 Hz; H5), 7.05–7.11 (m, 2H; Ar), 7.33 (s, 1H; NH), 7.35–7.43 (m, 2H; Ar), 8.16–8.23 (m, 1H; Ar); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.89, 22.87, 22.91, 41.10, 107.73, 121.36, 122.38, 126.30, 129.00, 129.84, 136.88, 140.05, 154.15, 189.22; HRMS *m*/*z* calcd $C_{14}H_{18}N_3OS_2$ $[M+H]^+$: 308.0886; found: 308.0890.

*4.3.3. N-(2-(4-Methyl-2-thioxothiazol-3(2H)-yl)phenyl)azepane-1-carboxamide (**3g**).* Yield: 67% (312 mg, white solid); mp 133–135 °C; R_f=0.39 (CH_2Cl_2/AcOEt, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41–1.84 (m, 8H; $(CH_2)_4$), 1.93 (d, 3H, *J*=1.2 Hz; CH_3), 3.27–3.55 (m, 4H; $N(CH_2)_2$), 6.36 (q, 1H, *J*=1.2 Hz; H5), 6.73 (s, 1H; NH), 7.04–7.16 (m, 1H; Ar), 7.18–7.32 (m, 1H; Ar), 7.42–7.57 (m, 1H; Ar), 7.91–

8.02 (m, 1H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.06, 26.92 (2C), 28.30 (2C), 46.88 (2C), 106.75, 124.84, 126.23, 127.32, 129.56, 130.59, 136.02, 141.08, 154.81, 188.63; HRMS *m*/*z* calcd $C_{17}H_{22}N_3OS_2$ $[M+H]^+$: 348.1199; found: 348.1200.

*4.3.4. 1,1-Diethyl-3-(2-(4-methyl-2-thioxothiazol-3(2H)-yl)phenyl) urea (**3h**).* Yield: 69% (299 mg, white solid); mp 129–131 °C; R_f=0.39 (CH_2Cl_2/AcOEt, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, 6H, *J*=7.1 Hz; $2CH_3$), 1.93 (d, 3H, *J*=1.1 Hz; CH_3), 3.06–3.50 (m, 4H; $N(CH_2)_2$), 6.36 (q, 1H, *J*=1.1 Hz; H5), 6.76 (s, 1H; NH), 7.04–7.16 (m, 1H; Ar), 7.17–7.30 (m, 1H; Ar), 7.42–7.56 (m, 1H; Ar), 7.96–8.06 (m, 1H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.68 (2C), 16.09, 41.65 (2C), 106.81, 124.60, 125.78, 127.31, 129.16, 130.59, 136.04, 141.06, 154.26, 188.60; HRMS *m*/*z* calcd $C_{17}H_{24}N_3OS_2$ $[M+H]^+$: 322.1042; found: 322.1044.

*4.3.5. 3-(2-(4-Methyl-2-thioxothiazol-3(2H)-yl)phenyl)-1,1-dipropyl-urea (**3i**).* Yield: 64% (302 mg, orange oil); R_f=0.29 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 6H, *J*=7.4 Hz; $2CH_3$), 1.38–1.63 (m, 4H; $2CH_2$), 1.92 (d, 3H, *J*=1.1 Hz; CH_3), 2.99–3.13 (m, 2H; NCH_2), 3.21–3.36 (m, 2H; NCH_2), 6.36 (q, 1H, *J*=1.1 Hz; H5), 6.74 (s, 1H; NH), 7.05–7.11 (m, 1H; Ar), 7.18–7.26 (m, 1H; Ar), 7.44–7.53 (m, 1H; Ar), 7.98–8.04 (m, 1H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.20 (2C), 16.08, 21.68 (2C), 49.34 (2C), 106.76, 124.55, 125.73, 127.29, 129.03, 130.56, 136.09, 141.04, 154.63, 188.63; HRMS *m*/*z* calcd $C_{17}H_{24}N_3OS_2$ $[M+H]^+$: 350.1355; found: 350.1353.

4.4. General procedure for the preparation of thiazolium salts 1a–e

To a solution of urea **3** (100 mg; **3a** 0.29 mmol, **3b** 0.28 mmol, **3c** 0.21 mmol, **3d** 0.26 mmol, **3e** 0.20 mmol) in CH_3CN (5 mL), CH_3I (10 equiv) was added and the solution stirred at room temperature. After 24 h the solvent was partially evaporated and the resulting solid filtered off.

*4.4.1. 4-Methyl-2-(methylthio)-3-(2-(3-phenylureido)phenyl)thiazol-3-ium iodide (**1a**).* Yield: 97% (137 mg, white solid); mp 156–158 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.30 (d, 3H, *J*=1.1 Hz; CH_3), 2.97 (s, 3H; CH_3), 6.99–7.07 (m, 1H; Ar), 7.22–7.55 (m, 6H; Ar), 7.70–7.75 (m, 1H; Ar), 7.86 (q, 1H, *J*=1.1 Hz; H5), 8.05–8.08 (m, 1H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 14.29, 18.40, 118.07, 120.30 (2C), 124.34, 126.50, 126.86, 127.22, 129.01, 129.91 (2C), 134.16, 136.25, 139.85, 148.34, 154.28, 181.99; HRMS *m*/*z* calcd $C_{18}H_{18}N_3OS_2^+$ $[M-I]^+$: 356.0885; found: 356.0884.

*4.4.2. 4-Methyl-2-(methylthio)-3-(2-(3-p-tolylureido)phenyl)thiazol-3-ium iodide (**1b**).* Yield: 97% (136 mg, white solid); mp 137–139 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.28 (s, 3H; CH_3), 2.30 (d, 3H, *J*=1.1 Hz; CH_3), 2.96 (s, 3H; CH_3), 7.06–7.11 (m, 2H; Ar), 7.20–7.24 (m, 2H; Ar), 7.40–7.52 (m, 2H; Ar), 7.69–7.75 (m, 1H; Ar), 7.85 (q, 1H, *J*=1.1 Hz; H5), 8.02–8.05 (m, 1H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 14.26, 18.28, 20.78, 111.00, 117.89, 120.62 (2C), 126.42, 126.81, 128.94, 130.38 (2C), 134.18, 136.38, 137.13, 139.42, 148.47, 165.40, 181.89; HRMS *m*/*z* calcd $C_{19}H_{20}N_3OS_2$ $[M-I]^+$: 370.1042; found: 370.1041.

*4.4.3. 3-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)phenyl)-4-methyl-2-(methylthio)thiazol-3-ium iodide (**1c**).* Yield: 97% (126 mg, white solid); mp 186–188 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.21 (d, 3H, *J*=0.9 Hz; CH_3), 2.93 (s, 3H; CH_3), 7.42–7.48 (m, 1H; Ar), 7.61–7.66 (m, 1H; Ar), 7.68 (br s, 1H; Ar), 7.70–7.75 (m, 1H; Ar), 8.04 (q, 1H, *J*=0.9 Hz; H5), 8.07 (br s, 2H; Ar), 8.09–8.12 (m, 1H; Ar), 8.60 (s, 1H; NH), 9.45 (s, 1H; Ar); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.65, 17.98, 114.99 (1C, sept, *J*=3 Hz), 118.10, 118.01–118.23 (m, 2C), 123.16 (2C, q, *J*=273 Hz), 124.71, 125.35, 125.58, 128.11, 130.74 (2C, q, *J*=33 Hz), 132.67, 134.22, 141.05, 145.80, 152.10, 179.72; HRMS *m*/*z* calcd $C_{20}H_{16}F_6N_3OS_2$ $[M-I]^+$: 492.0634; found: 492.0629.

*4.4.4. 4-Methyl-2-(methylthio)-3-(2-(3-(4-nitrophenyl)ureido)-phenyl)thiazol-3-ium iodide (**1d**).* Yield: 98% (134 mg, white solid); mp 183–185 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.21 (d, 3H, *J*=1.1 Hz; CH_3), 2.93 (s, 3H; CH_3), 7.42–7.47 (m, 2H; Ar), 7.61–7.67 (m, 3H; Ar), 8.04 (q, 1H, *J*=1.1 Hz; H5), 8.08–8.12 (m, 1H; Ar), 8.16–8.22 (m, 2H; Ar), 8.53 (s, 1H; NH), 9.47 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.68, 17.86, 117.80 (2C), 117.95, 124.51, 125.13 (2C), 125.31, 125.57, 128.09, 132.73, 134.32, 141.48, 145.45, 145.94, 151.70, 179.73; HRMS *m*/*z* calcd $C_{18}H_{17}N_4O_3S_2$ $[M-I]^+$: 401.0737; found: 401.0734.

*4.4.5. 3-(2-(3-(3,5-Bis(trifluoromethyl)benzyl)ureido)phenyl)-4-methyl-2-(methylthio)thiazol-3-ium iodide (**1e**).* Yield: 99% (127 mg, white solid); mp 177–179 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.24 (d, 3H, *J*=1.1 Hz; CH_3), 2.94 (s, 3H; CH_3), 4.43 (d, 1H, *J*=19.8 Hz; CH_A), 4.49 (d, 1H, *J*=19.8 Hz; CH_B), 7.38–7.52 (m, 2H; Ar), 7.66–7.72 (m, 1H; Ar), 7.76 (q, 1H, *J*=1.1 Hz; H5), 7.85–7.93 (m, 4H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 14.23, 18.40, 43.75, 117.81, 121.89 (1C, sept, *J*=4 Hz), 124.86 (2C, q, *J*=272 Hz), 126.67, 126.85, 127.53, 128.92 (2C, q, *J*=4 Hz), 129.00, 132.72 (2C, q, *J*=33 Hz), 134.11, 136.40, 144.53, 148.25, 157.15, 181.81; HRMS *m*/*z* calcd $C_{21}H_{18}F_6N_3OS_2$ $[M-I]^+$: 506.0790; found: 506.0800.

4.5. General procedure for the preparation of thiazolium salts 1f–n

Urea **3** (100 mg; **3a** 0.29 mmol, **3b** 0.28 mmol, **3e** 0.20 mmol, **3f** 0.33 mmol, **3 g** 0.29 mmol, **3 h** 0.31 mmol, **3i** 0.29 mmol) was suspended in the corresponding alkyl iodide (2 mL) and the mixture refluxed for 1 h under magnetic stirring. The resulting solid was then filtered off and washed with petroleum ether.

*4.5.1. 2-(Ethylthio)-4-methyl-3-(2-(3-phenylureido)phenyl)thiazol-3-ium iodide (**1f**).* Yield: 98% (143 mg, white solid); mp 119–121 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.52 (t, 3H, *J*=7.4 Hz; CH_3), 2.29 (d, 3H, *J*=1.1 Hz; CH_3), 3.46 (dq, 1H, *J*=7.4 Hz, J_{AB}=19.8 Hz; CH_A), 3.53 (dq, 1H, *J*=7.4 Hz, J_{AB}=19.8 Hz; CH_B), 6.99–7.06 (m, 2H; Ar), 7.21–7.59 (m, 6H; Ar), 7.68–7.77 (m, 1H; Ar), 7.86 (q, 1H, *J*=1.1 Hz; H5), 8.01–8.08 (m, 1H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 13.27, 14.35, 31.83, 118.12, 120.30 (2C), 124.33, 126.64, 126.89, 127.50, 129.03, 129.90 (2C), 134.09, 136.14, 139.87, 148.04, 154.27, 180.19; HRMS *m*/*z* calcd $C_{19}H_{20}N_3OS_2$ $[M-I]^+$: 370.1042; found: 370.1042.

*4.5.2. 2-(Ethylthio)-4-methyl-3-(2-(3-p-tolylureido)phenyl)thiazol-3-ium iodide (**1g**).* Yield: 94% (135 mg, white solid); mp 142–144 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.41 (t, 3H, *J*=7.3 Hz; CH_3), 2.19 (d, 3H, *J*=0.9 Hz; CH_3), 2.23 (s, 3H; CH_3) 3.45 (q, 2H, *J*=7.3 Hz; SCH_2), 7.04–7.12 (m, 2H; Ar), 7.23–7.30 (m, 2H; Ar), 7.31–7.40 (m, 1H; Ar), 7.54–7.61 (m, 1H; Ar), 7.62–7.72 (m, 1H; Ar); 8.07 (q, 1H, *J*=0.9 Hz; H5), 8.10–8.16 (m, 1H; Ar), 8.16 (br s, 1H; NH), 8.69 (br s, 1H; NH); ^{13}C NMR (75 MHz, CD_3OD) δ 12.92, 13.70, 20.35, 30.09, 118.12, 118.60 (2C), 123.66, 124.53, 124.55, 127.95, 129.29 (2C), 131.42, 132.58, 135.02, 136.27, 145.85, 151.95, 177.86; HRMS *m*/*z* calcd $C_{20}H_{22}N_3OS_2$ $[M-I]^+$: 384.1199; found: 384.1202.

*4.5.3. 3-(2-(3-(3,5-Bis(trifluoromethyl)benzyl)ureido)phenyl)-2-(ethylthio)-4-methylthiazol-3-ium iodide (**1h**).* Yield: 96% (126 mg, white solid); mp 179–181 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.49 (t, 3H, *J*=7.4 Hz; CH_3), 2.25 (d, 3H, *J*=1.1 Hz; CH_3), 2.94 (s, 3H; CH_3), 3.44 (q, 2H, *J*=7.4 Hz; CH_2), 4.42 (d, 1H, *J*=19.8 Hz; CH_A), 4.49 (d, 1H, *J*=19.8 Hz; CH_B), 7.38–7.53 (m, 2H; Ar), 7.65–7.73 (m, 1H; Ar), 7.75 (q, 1H, *J*=1.1 Hz; H5), 7.84–7.92 (m, 4H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 13.27, 14.29, 31.77, 43.78, 117.73, 121.92 (1C, sept, *J*=4 Hz),

124.87 (2C, q, J=272 Hz), 126.93, 126.98, 127.88, 128.98 (2C, q, J=4 Hz), 129.01,132.72 (2C, q, J=33 Hz) 134.08, 136.35, 144.54, 148.06, 157.12, 179.99; HRMS m/z calcd $C_{22}H_{20}F_6N_3OS_2$ $[M-I]^+$: 520.0947; found: 520.0950.

*4.5.4. 2-(Ethylthio)-3-(2-(3-isopropylureido)phenyl)-4-methylthiazol-3-ium iodide(**1i**).* Yield: 99% (149 mg, white solid); mp 170–172 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.11 (d, 3H, J=6.5 Hz; CH_3), 1.13 (d, 3H, J=6.5 Hz; CH_3), 1.53 (t, 3H, J=7.4 Hz; CH_3), 2.26 (d, 3H, J=1.1 Hz; CH_3), 3.49 (q, 2H, J=7.4 Hz; SCH_2), 3.78 (sept, 1H, J=6.5 Hz; CH), 7.32–7.42 (m, 1H; Ar), 7.45–7.52 (m, 1H; Ar), 7.62–7.72 (m, 1H; Ar), 7.86 (q, 1H, J=1.1 Hz; H5), 7.93–7.99 (m, 1H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 12.69, 13.67, 22.50 (2C), 31.16, 42.57, 117.45, 125.49, 125.62, 126.37, 128.30, 133.35, 136.03, 147.37, 155.66, 179.50; HRMS m/z calcd $C_{16}H_{22}N_3OS_2$ $[M-I]^+$: 336.1199; found: 336.1199.

*4.5.5. 2-(Decylthio)-4-methyl-3-(2-(3-phenylureido)phenyl)thiazol-3-ium iodide (**1j**).* Yield: 96% (171 mg, white solid); mp 51–53 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 0.85–0.94 (m, 3H; CH_3), 1.19–1.52 (m, 14H; $(CH_2)_7$), 1.80–1.93 (m, 2H; CH_2), 2.30 (d, 3H, J=1.0 Hz; CH_3), 3.42–3.51 (m, 2H; SCH_2), 6.98–7.06 (m, 1H; Ar), 7.21–7.30 (m, 2H; Ar), 7.33–7.54 (m, 4H; Ar), 7.68–7.76 (m, 1H; Ar), 7.85 (q, 1H, J=1.0 Hz; H5), 7.99–8.05 (m, 1H; Ar); ^{13}C NMR (75 MHz, CD_3OD) δ 14.37, 14.42, 23.71, 28.90, 29.74, 30.07, 30.37, 30.48, 30.60, 33.02, 37.31, 117.98, 120.27 (2C), 124.33, 126.69, 126.93, 127.58, 129.00, 129.92 (2C), 134.11, 136.14, 139.89, 148.14, 154.22, 180.34, HRMS m/z calcd $C_{27}H_{36}N_3OS_2$ $[M-I]^+$: 482.2294; found: 482.2296.

*4.5.6. 2-(Decylthio)-4-methyl-3-(2-(3-p-tolylureido)phenyl)thiazol-3-ium iodide (**1k**).* Yield: 97% (170 mg, white solid); mp 147–149 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78–0.97 (m, 3H; CH_3), 1.12–1.52 (m, 14H; $(CH_2)_7$), 1.73–1.97 (m, 2H; CH_2), 2.24 (d, 3H, J=0.9 Hz; CH_3), 2.26 (s, 3H; CH_3), 3.20–3.68 (m, 2H; SCH_2), 6.96–7.13 (m, 3H; Ar), 7.16–7.26 (m, 1H; Ar), 7.44–7.70 (m, 4H; Ar+H5), 7.68–7.76 (m, 1H, Ar), 8.29–8.42 (m, 1H; Ar), 8.50 (s, 1H; NH), 9.20 (s, 1H; NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.05, 14.50, 20.73, 22.60, 27.49, 28.74, 28.92, 29.18, 29.24, 29.40, 31.79, 37.29, 117.18, 118.94, 123.82, 124.11, 125.88, 126.37, 129.11, 131.99, 132.97, 135.73, 136.43, 146.09, 152.67, 179.19; HRMS m/z calcd $C_{28}H_{38}N_3OS_2$ $[M-I]^+$: 496.2451; found: 496.2457.

4.6. General procedure for the preparation of *S*-alkylcarbamothioates 2a–k

To a solution of thiazolium salt **1** (100 mg; **1a** 0.21 mmol, **1b** 0.20 mmol, **1c** 0.16 mmol, **1d** 0.19 mmol, **1e** 0.16 mmol, **1f** 0.29 mmol, **1 g** 0.20 mmol, **1 h** 0.15 mmol, **1i** 0.22 mmol, **1j** 0.16 mmol, **1 k** 0.16 mmol) in CH_3CN (5 mL), NEt_3 (1 equiv) is added and the solution stirred at room temperature. After 15 min the solvent is evaporated and CH_2Cl_2 (15 mL) is added. The organic layer is then washed with brine (3×10 mL), dried over $MgSO_4$ and evaporated to dryness. The resulting *S*-alkylcarbamothioates **2** and thiazolobenzimidazole **7** are purified by silica gel chromatography (CH_2Cl_2/AcOEt, 9:1).

*4.6.1. S-Methyl phenylcarbamothioate (**2a**)[14,15].* Yield: 95% (33 mg, white solid); mp 77–79 °C; R_f=0.76 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H; CH_3), 6.99–7.21 (m, 2H; NH and Ar), 7.27–7.46 (m, 4H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.62, 119.73 (2C), 124.44, 129.13 (2C), 137.69, 166.23; HRMS m/z calcd $C_8H_{10}NOS$ $[M+H]^+$: 168.0478; found: 168.0472.

*4.6.2. S-Methyl p-tolylcarbamothioate (**2b**)[15].* Yield: 94% (34 mg, white solid); mp 107–109 °C; R_f=0.87 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H; CH_3), 2.41 (s, 3H; CH_3), 7.03 (br s, 1H; NH), 7.08–7.33 (m, 4H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.60, 20.84, 120.12 (2C), 129.62 (2C), 134.28, 135.06, 166.35; HRMS m/z calcd $C_9H_{12}NOS$ $[M+H]^+$: 182.0634; found: 182.0632.

*4.6.3. S-Methyl 3,5-bis(trifluoromethyl)phenylcarbamothioate (**2c**).* Yield: 93% (45 mg, white solid); mp 111–113 °C; R_f=0.74 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.47 (s, 3H; CH_3), 7.31 (br s, 1H; NH), 7.60 (s, 1H; Ar), 7.94 (s, 2H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.69, 117.47 (sept, 1C; J=4 Hz), 118.90 (q, 2C; J=3 Hz), 122.95 (q, 2C; J=273 Hz), 132.57 (q, 2C; J=33 Hz); 139.06, 166.98; HRMS m/z calcd $C_{10}H_6F_6NOS$ $[M-H]^-$: 302.0080; found: 302.0081.

*4.6.4. S-Methyl 4-nitrophenylcarbamothioate (**2d**)[16].* Yield: 96% (39 mg, white solid); mp 197–199 °C; R_f=0.65 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H; CH_3), 7.35 (br s, 1H; NH), 7.56–7.64 (m, 2H; Ar), 8.18–8.25 (m, 2H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.77, 118.47 (2C), 125.31 (2C), 143.36, 143.44, 166.73; HRMS m/z calcd $C_8H_7N_2O_3S$ $[M-H]^-$: 211.0183; found: 211.0182.

*4.6.5. S-Methyl 3,5-bis(trifluoromethyl)benzylcarbamothioate (**2e**).* Yield: 96% (48 mg, white solid); mp 87–89 °C; R_f=0.69 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H; CH_3), 4.59 (d, 2H, J=6.1 Hz; CH_2), 5.91 (br s, 1H; NH), 7.68–7.83 (m, 3H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.43, 44.32, 121.63 (1C, sept; J=4 Hz), 123.13 (2C, q; J=273 Hz), 127.61 (2C, q; J=3 Hz), 132.03 (2C, q; J=33 Hz); 140.58, 168.79; HRMS m/z calcd $C_{11}H_8F_6NOS$ $[M-H]^-$: 316.0236; found: 316.0237.

*4.6.6. S-Ethyl phenylcarbamothioate (**2f**)[15].* Yield: 93% (34 mg, white solid); mp 71–73 °C; R_f=0.79 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, J=7.4 Hz; CH_3), 2.99 (q, 2H, J=7.4 Hz; CH_2), 7.06 (br s, 1H; NH), 7.06–7.15 (m, 1H; Ar), 7.27–7.48 (m, 4H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.54, 24.69, 119.73 (2C), 124.35, 129.09 (2C), 137.72, 165.87; HRMS m/z calcd $C_9H_{12}NOS$ $[M+H]^+$: 182.0634; found: 182.0634.

*4.6.7. S-Ethyl p-tolylcarbamothioate (**2g**)[15].* Yield: 96% (37 mg, white solid); mp 79–81 °C; R_f=0.82 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, J=7.4 Hz; CH_3), 2.33 (s, 3H; CH_3), 2.99 (q, 2H, J=7.4 Hz; CH_2), 7.07 (br s, 1H; NH), 7.10–7.32 (m, 4H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.55, 20.81, 24.64, 120.01 (2C), 134.18, 135.11, 165.83; HRMS m/z calcd $C_{10}H_{14}NOS$ $[M+H]^+$: 196.0791; found: 196.0796.

*4.6.8. S-Ethyl 3,5-bis(trifluoromethyl)benzylcarbamothioate (**2h**).* Yield: 94% (56 mg, white solid); mp 73–75 °C; R_f=0.74 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.4 Hz; CH_3), 2.96 (q, 2H, J=7.4 Hz; CH_2), 4.59 (q, 2H, J=6.1 Hz; CH_2), 5.80 (br s, 1H; NH), 7.70–7.85 (m, 3H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ=15.53, 24.58, 44.21, 121.57 (1C, sept; J=4 Hz), 123.14 (2C, q; J=273 Hz), 127.58 (2C, q; J=3 Hz), 132.02 (2C, q; J=33 Hz); 140.64, 168.39; HRMS m/z calcd $C_{12}H_{10}F_6NOS$ $[M-H]^-$: 330.0393; found: 330.0390.

*4.6.9. S-Ethyl isopropylcarbamothioate (**2i**)[8].* Yield: 97% (31 mg, white solid); mp 60–62 °C; R_f=0.80 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, 6H, J=6.5 Hz; $2CH_3$), 1.26 (t, 3H, J=7.4 Hz; CH_3), 2.88 (q, 2H, J=7.4 Hz; SCH_2), 3.76–4.25 (m, 1H; CH), 5.26 (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.66, 22.77 (2C), 24.15, 43.56, 166.14; HRMS m/z calcd $C_6H_{13}NOS$ $[M+H]^+$: 148.0791; found: 148.0790.

*4.6.10. S-Decyl phenylcarbamothioate (**2j**)[17].* Yield: 97% (47 mg, white solid); mp 64–66 °C; R_f=0.70 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.90 (m, 3H; CH_3), 1.20–1.43 (m, 14H; $(CH_2)_7$), 1.62–1.70 (m, 2H; CH_2), 2.97 (t, 2H, J=7.3 Hz; SCH_2), 7.00 (br

s, 1H; NH), 7.07–7.13 (m, 1H; Ar), 7.29–7.34 (m, 2H; Ar), 7.39–7.43 (m, 2H; Ar); ^{13}C NMR (DeptQ 135, 125 MHz, $CDCl_3$) δ 14.10, 22.66, 28.77, 29.12, 29.28, 29.50, 29.52, 30.28, 30.36, 31.87, 119.64 (2C), 124.33, 129.11 (2C), 137.78, 165.90; HRMS *m*/*z* calcd $C_{17}H_{28}NOS$ $[M+H]^+$: 294.1886; found: 294.1884.

*4.6.11. S-Decyl p-tolylcarbamothioate (**2k**).* Yield: 95% (47 mg, white solid); mp 66–68 °C; R_f=0.85 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H; CH_3), 1.18–1.46 (m, 14H; $(CH_2)_7$), 1.57–1.73 (m, 2H; CH_2), 2.31 (s, 3H; CH_3), 2.96 (t, 2H, *J*=7.3 Hz; SCH_2), 6.98 (br s, 1H; NH), 7.08–7.15 (m, 2H; Ar), 7.25–7.32 (m, 2H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.10, 20.83, 22.66, 28.78, 29.13, 29.29, 29.50, 29.52, 30.31 (2C), 31.87, 119.90, 129.59, 134.12, 135.16,165.88; HRMS *m*/*z* calcd $C_{18}H_{30}NOS$ $[M+H]^+$: 308.2042; found: 308.2041.

4.7. General procedure for the preparation of *S*-alkylcarbamothioates 2l–n

To a solution of urea **3** (100 mg; **3g** 0.29 mmol, **3h** 0.31 mmol, **3i** 0.29 mmol) EtI (1.5 mL) is added and the solution stirred at room temperature for 24 h. The solvent is evaporated and the resulting solid (used without further purification) is solubilised in CH_3CN (5 mL). Then, NEt_3 (1 equiv) is added and the solution stirred at room temperature. After 15 min the solvent is evaporated and the resulting *S*-alkylcarbamothioates **2** and thiazolobenzimidazole **7** are purified by silica gel chromatography (CH_2Cl_2/AcOEt, 9:1).

*4.7.1. S-Ethyl azepane-1-carbothioate (Molinate) (**2l**)*[5f,18]. Yield: 95% (51 mg, colourless oil); R_f=0.85 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J*=7.4 Hz; CH_3), 1.47–1.62 (m, 4H; $2CH_2$), 1.73 (br s, 4H; $2CH_2$), 2.89 (q, 2H, *J*=7.4 Hz; SCH_2), 3.43 (t, 2H, *J*=6.0 Hz; NCH_2), 3.54 (t, 2H, *J*=6.0 Hz; NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.33, 24.52, 26.93, 27.16, 27.85, 28.35, 47.25, 47.58, 167.76.

*4.7.2. S-Ethyl diethylcarbamothioate (Ethiolate) (**2m**)*[5f,18]. Yield: 96% (48 mg, colourless oil); R_f=0.82 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (br s, 6H; $2CH_3$), 1.27 (t, 3H, *J*=7.4 Hz; CH_3), 2.89 (q, 2H, *J*=7.4 Hz; SCH_2), 3.37 (br s, 4H; $N(CH_2)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.37 (2C), 15.34, 24.47, 41.88 (2C), 167.20.

*4.7.3. S-Ethyl dipropylcarbamothioate (EPTC) (**2n**)*[5f,18]. Yield: 96% (52 mg, colourless oil); R_f=0.83 (CH_2Cl_2/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 6H, *J*=7.4 Hz; $2CH_3$), 1.27 (t, 3H, *J*=7.4 Hz; CH_2), 1.59 (br s, 4H; $2CH_2$), 2.88 (q, 2H, *J*=7.4 Hz; SCH_2), 3.26 (br s, 4H; $N(CH_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.22 (2C), 15.34, 21.13, 21.54, 24.57, 49.05, 49.60, 167.76.

4.8. 3-Methyl-thiazolo[3,2-*a*]benzimidazole (7)[3]

For entries **2a**–**n**, the isolated yield in **7** was always larger than 95%.

4.9. Procedure for the cross reaction

To a solution of thiazolium salts **1a** (0.065 mmol) and **1k** (0.065 mmol) in methanol (3 mL), NEt_3 (1 equiv, 0.130 mmol) was added and the solution stirred at room temperature for 30 min. Then, the solvent was evaporated and the crude resulting solid recovered and analysed by mass spectroscopy, four peaks corresponding the **2a**, **2k**, **2b** and **2j** were observed. ESI-MS *m*/*z* $[M+H]^+$: 168 (**2a**), 182 (**2b**), 189 (**7**), 294 (**2j**), 308 (**2k**); $[M+Na]^+$: 190 (**2a**), 204 (**2b**), 211 (**7**), 316 (**2j**), 330 (**2k**).

Acknowledgements

ALD and MAM are grateful to BFA program (French-Algerian exchange program) for grants.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.020.

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