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A new procedure for thioester deprotection using thioglycolic acid in both homogeneous and heterogeneous phase

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ABSTRACT

Classic acetyl thioester protection/deprotection methodologies are widely used in organic synthesis, but deprotection step usually requires harsh conditions not suitable for labile substrates. In this work, a new method for thioester deprotection using a thiotransesterification approach is described. Firstly, thioglycolic acid (TGA) was identified as a good deprotecting reagent in solution. In order to develop a thiol polymer-supported reagent, TGA was anchored to a PEG-based resin through an amide bond (TG-NCO-SH). Both homogeneous and heterogeneous approaches were conveniently carried out at room temperature, in aqueous buffer at pH 8. The mild conditions were suitable for alkyl and phenyl thioesters. Moreover labile thioesters containing thiazolidine and oxazolidine scaffolds, bearing amine, ester and acetal functionalities were also deprotected. The polymer-supported TGA gave better deprotection yields compared to TGA in solution, yields ranging from 61 to 90%. The feasibility of the recovery and reuse of TG-NCO-SH reagent was explored, showing it can be reused at least five times without lossing the activity.

1. Introduction

Thiols are important functional groups present in many bioactive compounds, including drugs and natural flavors, see examples in Fig. 1. Captopril **1** and zofenopril **2** are drugs approved as ACE inhibitors for treatment of hypertension [1], and tiopronin **3** is a drug used for cystinuria [2]. Thiorphan **4**, the active metabolite of racecadotril, is an enkephalinase inhibitor and exhibits antidiarrheal effects in human [3]. Dimercaprol **5** is a copper chelating agent that has been approved by the FDA to treat Wilson's disease [4]. Volatile thiols are key aroma components present in many foods like meat (3-mercapto-2-butanone **6**), coffee (furfurylthiol **7**), and grapefruit (1-p-menthene-8-thiol **8**) among others [5,6].

Bisthiazolidines **9** have been described as bicyclic compounds containing a free thiol able to inhibit metallo-β-lactamases (MBL). Mechanistically, bisthiazolidines were designed as penicillin analogs. These compounds demonstrated competitive inhibition of all MBL subclasses, with *Ki* values in the micromolar range against NDM-1, VIM-2, Sfh-I, L1, IMP-1, GOB-18 and BcII, MBL of clinical importance. [7–9].

Previous studies showed that the mercaptomethyl group present in **9** is essential for MBL inhibition. However, the importance of the carboxylic acid is unexplored. Aiming to prepare new bisthiazolidine analogs with variations at the carboxylic acid, we decided to explore a suitable strategy for thiol protection/deprotection. In particular, bisthiazolidines **9** require mild conditions for deprotection to avoid thiazolidine ring opening or dimerization.

Acyl groups have been widely used as synthetically useful thiol protecting groups due to its preparation under mild conditions in very good yields. Although there are numerous deprotection methods described, many involve harsh conditions and are accompanied by significant formation of disulfides when labile substrates are used. Reported conditions include strong bases like NaOH [10], NH_3 in MeOH [11], or MeONa [12]. These methods typically produce better results when aliphatic and unfunctionalized substrates are used [13].

In the last years, new milder and chemoselective methods have been developed for thioester hydrolysis. Among others, it was reported the use of tetrabutylammonium cyanide [14] and TiCl4/Zn [15] for deprotection of acetyl thioesters.

We focused on the potential of the transthioesterification

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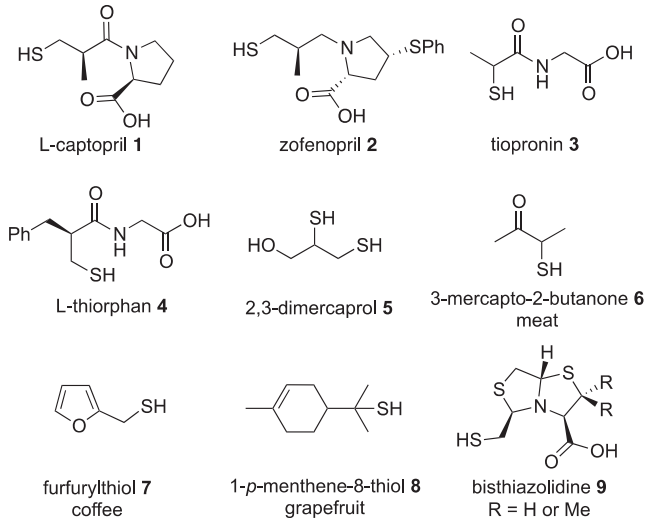


Fig. 1. Thiol-containing compounds known as drugs or flavors (**1**–**8**) and bisthiazolidine **9**.

process for thioester deprotection, a reversible reaction between a thioester and a thiol in the presence of a base or strongly activated thiolate leaving group [16]. Transthioesterification is also well described as the first step in Native Chemical Ligation, a widely used technique for amide bond formation in peptide and protein solid-phase synthesis [17]. To the best of our knowledge, there are no methodologies reported using thiols for thioester deprotection in solution.

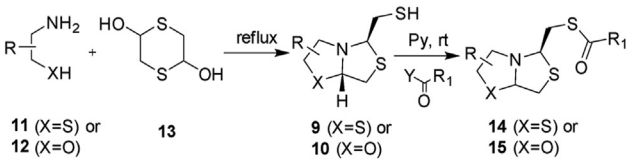
Since thiol-thioester exchange is an equilibrium, the thiol used for deprotection should be used in excess to drive the equilibrium toward the desired product. In this case, when the reaction is performed in homogeneous solution-phase, the purification step could be troublesome. Exploring an alternative approach that simplifies the purification step, we aimed to develop a polymer-supported reagent for heterogeneous solution-phase able to deprotect thioesters through thiol-thioester exchange.

In recent years, synthesis using polymer-supported reagents and scavengers has become a powerful tool. Unlike solid-phase synthesis, the polymer-supported reagent produces a chemical transformation on the substrate present in solution [18]. This approach has advantages over conventional solution-phase synthesis such as the easier separation of the supported species from the reaction mixture by filtration and the use of excess reagent to force the reaction to completion without causing work-up problems. In addition, it has the advantage of solution-phase synthesis since it allows monitoring the reaction progress easily by using conventional techniques, such as TLC or HPLC, avoiding the cleavage step of solid-phase chemistry [19].

In this context, we explored the use of thiols for thioester deprotection through thiol-thioester exchange in aqueous media, both in conventional homogeneous solution-phase and heterogeneous solution-phase through anchoring the thiol to a solid support.

2. Results and discussion

Bisthiazolidines **9a-e** and oxazolidinylthiazolidines **10a-b** were obtained by double cyclization of 2-aminothiols **11** or 2-aminoalcohols **12** with two molecules of mercaptoacetaldehyde, commercially available as dithiane **13**, as described in our previous work (Scheme 1) [20–22]. Then, S-acetyl bisthiazolidines **14a-e** and S-acetyl oxazolidinylthiazolidines **15a-b** were easily prepared



Scheme 1. Synthesis of thioesters **14a-g** and **15a-b**.

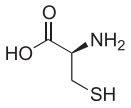
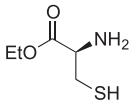
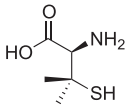
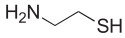
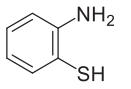
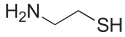
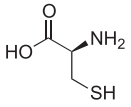
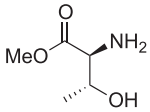
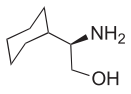
using Ac_2O and Py at room temperature with yields ranging from 62 to 89% (Table 1). The compounds S-butyryl **14f** and S-benzoyl **14g** were obtained using the corresponding acyl chloride and TEA in CH_2Cl_2 in 69 and 72% yield, respectively.

2.1. Deprotection optimization

S-acetyl bisthiazolidine **14a** was selected as a model to study the optimal deprotection conditions. Firstly, general methods described in literature for thioacetyl deprotection were employed, see Table 2. When NaOH [10], NH_3 in MeOH [11] and NaSMe in CH_2Cl_2[23] were used, decomposition of the starting material was observed (Table 2, entry 1, 3 and 4, respectively). Thiol **9a** was obtained when using $NH_2OH{\cdot}HCl$ and TEA in MeOH [24] but in low yield (33%), Table 2, entry 2.

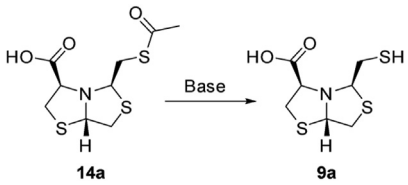
These results prompted us to investigate an alternative methodology for thioester deprotection. Thus, we explored the usefulness of different commercially available thiols with a broad range of

Table 1
Synthesis of thioesters **14a-g** and **15a-b**.

Entry	Starting material		Y	R_1	Product, Yield (%)[a]
1		**11a**	OAc	Me	**14a**, 89
2		**11b**	OAc	Me	**14b**, 71
3		**11c**	OAc	Me	**14c**, 62
4		**11d**	OAc	Me	**14d**, 65
5		**11e**	OAc	Me	**14e**, 79
6		**11d**	Cl	*n*-butyl	**14f**, 69
7		**11a**	Cl	Ph	**14g**, 72
8		**12a**	OAc	Me	**15a**, 62
9		**12b**	OAc	Me	**15b**, 79

[a] Isolated yields after chromatographic column purification.

Table 2
Basic conditions used for deprotection of **14a**.



Entry	Conditions	Yield (%)[a]
1	NaOH 0.2 M, EtOH	dec[b]
2	$NH_2OH{\cdot}HCl$, TEA, MeOH	33%
3	MeOH, NH_3	dec[b]
4	NaSMe, CH_2Cl_2	dec[b]

[a] Isolated yields after chromatographic column purification.
[b] dec = starting material decomposition.

pKa values, for deprotection of thioester **14a** through thiol-thioester exchange, see Scheme 2. The reaction was performed in aqueous buffer at pH 8 to ensure a high concentration of thiolate. Since thiol−thioester exchange is an equilibrium, deprotecting agents were used in excess (2 equivalents) to drive the equilibrium toward the desired product **9a**. In order to rapidly find the best thiol for deprotection, the reaction time was set at 30 min, see Scheme 2.

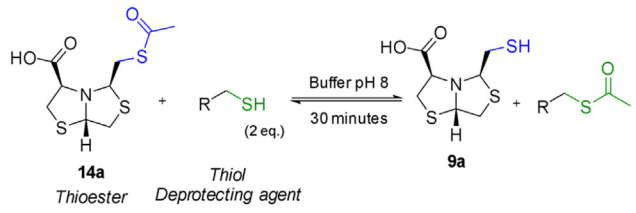
Different thiols were selected for the screening: alkyl thiols such as thioglycolic acid (TGA), *n*-propanethiol and β-mercaptoethanol (ME) and aromatic thiols like thiophenol and 2-NH_2-4-Cl-thiophenol. Redox reagents like reduced dithiothreitol (DTT) and reduced glutathione were also explored. With the aim to verify that deprotection does not occur in absence of the thiol, incubation of **14a** in PB pH 8 at rt for 6 h was performed, and detection of **9a** was not observed (Table 3, entry 8).

Thiol pKa value does not correlate directly with the deprotection compound potential as shown in Table 3. The best result was obtained for TGA (56%, Table 3, entry 1), while the free thiol **9a** was not observed using *n*-propanethiol, thiophenol or 2-NH_2-4-Cl-thiophenol, (Table 3, entries 2, 4 and 5). Reduced glutathione and DTT, bearing both a high negative redox potential and high aqueous solubility, were used and deprotection was only observed for the last one with 49% yield (Table 3, entries 6).

Based on the results obtained, thioglycolic acid was selected as the deprotecting agent and the reaction time was extended to 24 h. We found a complete conversion of **14a** to **9a** after 24 h at room temperature and 74% yield after chromatographic column purification (Table 6, entry 1).

Once we found that TGA was suitable for deprotection of acetyl-thioester **14a** in solution, we decided to apply a solid-supported approach, based on the advantages it presents such as simplification of product work-up, purification and catalyst recycling.

Several polymer-supported deprotecting agents were recently reported. Kobayashi and col. described a polystyrene-supported sulfonic acid reagent able to hydrolyze thioesters in refluxing water [30]. Nevertheless, these conditions result too harsh for the bisthiazolidine heterocycle. Furthermore, Liguori and col prepared



Scheme 2. S-acetyl deprotection through thiol-thioester exchange.

Table 3
Screening of thiols for the deprotection reaction of **14a** in PB pH 8 in 30'.

Entry	Additive (2eq)	pKa	Yield 9a (%)[a]
1	Thioglycolic acid (TGA)	10.6 [25]	56
2	*n*-propanethiol	10.8 [26]	8
3	β-Mercaptoethanol (ME)	9.5 [25]	31
4	Thiophenol	6.4 [27]	7
5	2-NH_2-4-Cl-thiophenol	5.7 [28]	0
6	Dithiothreitol (DTT)	9.2 [25]	49
7	Glutathione	8.8 [29]	0
8	No additive	–	0

[a] Isolated yields after column chromatography purification.

a polymer-supported TGA useful for the deprotection of N-nosyl-protected α-amino acids. The reaction is carried out in DCM, using a Wang resin as solid support [31].

Based on this background, we aimed to develop a different solid-supported reagent suitable for S-acetyl deprotection in mild conditions. In this sense, we selected PEG-based resins which have a broad solvent compatibility and are known to tolerate aqueous−organic solvent systems. In particular, polymers based on Tentagel® (TG) resin have gained considerable importance in recent years. They provide significant stability to mechanical, chemical, and thermal demands under diverse operating conditions and multiple rounds of synthetic transformations [32,33].

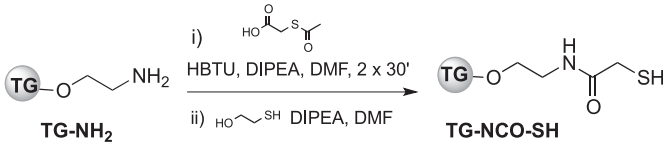
A variety of TentaGel® (TG) resins are commercially available for synthesis and screening. Firstly, we used TG thiol resin (TG-S-SH, 0.2−0.3 meq/g, 130 μm) which is terminally functionalized with a thiol. We envisioned that TG-S-SH resin could be useful for thioester deprotection through thiol/thioester exchange, in analogy with thioglycolic acid in solution. Thus, we performed the exchange reaction using 2 equivalents of TG-S-SH resin and S-acetyl bisthiazolidine **14a** as starting material, in MeOH:phosphate buffer (PB) pH 8 (1:9) at rt, but **9a** was not detected after 24 h.

Since the distance between the thiol and the solid support could be critical for the deprotection reaction, we decided to explore the use of a resin-linker system. This allows the introduction of an active group that is separated from the insoluble polymer.

We envisioned that commercially available aminomethylated resin (TG-NH_2) could be rapidly functionalized with a linker containing thiol. Based on the results obtained in homogeneous solution-phase, we selected TGA as a thiol-containing linker and connected to the resin through an amide bond. The resin was readily converted to the corresponding amido-mercapto resin (TG-NCO-SH) in two steps, see Scheme 3.

First, thiol-protected thioglycolic acid was incorporated into the solid support following a standard coupling protocol using an excess of HBTU [34]. The acylation reaction was >99% complete after 2 × 30 min couplings as indicated by quantitative ninhydrin analysis [35], after which residual free amine groups were capped by treatment with acetic anhydride in DMF [36]. Secondly, the TG-NCO-SH resin was generated by thiolytic cleavage employing a described method for solid phase (2-mercaptoethanol/DIPEA/DMF 1:1:18) [37].

Thus, using this two-step solid-phase procedure, it was possible to convert the aminomethylated resin (TG-NH_2) into the



Scheme 3. Synthesis of polymer-supported TGA.

corresponding amido-mercapto resin (TG-NCO-SH) in about 3 h. The thiol loading was determined using the methodology reported by Badyal et al. based on Ellman's reagent [38]. We found that the resin load was 0.35 mmol/g after 3 × 20 min cycles.

The usefulness of the TG-NCO-SH resin as a deprotecting agent was studied. The exchange reaction was performed using 2 equivalents of TG-NCO-SH resin previously generated and S-acetyl bisthiazolidine **14a** as starting material in MeOH:PB pH 8 (1:9), see Scheme 4. At suitable intervals aliquots were taken for HPLC analysis. After 24 h, the conversion of **14a** into **9a** was >99%, and the yield 93% (calculated by HPLC), see Table 4, entry 3.

Once the optimal time was set, the reaction was scaled up for the deprotection of **14a** using 2 equivalents of the TG-NCO-SH. After 24 h, the reaction was completed (verified by TLC), and the product was obtained after simple filtration and extraction. Thus, **9a** was obtained in 93% yield without any further purification.

2.2. Resin recycling

The successful recovery and reuse of catalysts is an essential aspect of green chemistry and it determines its potential value for large-scale operation. In recent years, the chemical recycling of waste polymers has received a great deal of attention [39]. Thus, the potential chemical recycling of TG-NCO-SH resin was explored.

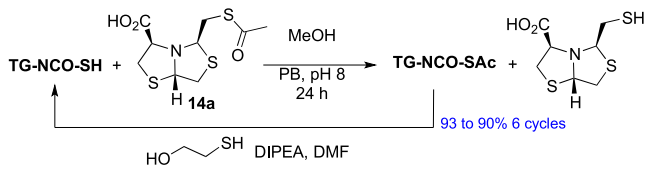
In order to evaluate the resin recovery, several cycles of regeneration-reuse were performed. At the end of the reaction the resin was washed completely with MeOH and completely regenerated by thiolytic cleavage, as indicated by thiol quantification based on Ellman's reagent. This method is useful to determine resin load since it is specific for free thiols in their reductive state [38]. Then, the resin was washed and reused for the subsequent cycles. Deprotection of the linked thiol must be done right before its use to prevent any oxidation processes.

Five additional cycles of **14a** deprotection were performed, and after 24 h we obtained **9a** in 93%, 90%, 89%, 90% and 87% yields for successive cycles, calculated by HPLC, Table 5, entries 2 to 6. The results demonstrated that TG-NCO-SH resin can be reused at least five times without significatively losing the activity.

2.3. Scope of the reaction in homogeneous and heterogeneous phase

In order to explore the scope of the reaction, twelve substrates were tested including aliphatic and aromatic thiols. The reaction was carried out in both homogeneous and heterogeneous phase and the yields were compared, see Table 6. Deprotection was performed using 2 equivalents of TGA or TG-NCO-SH respectively, in PB at pH 8 during 24 h at room temperature. The resin (TG-NCO-SH) was regenerated by thiolytic cleavage and employed for subsequent deprotections.

The results obtained show that deprotection of S-acyl bisthiazolidines **14a-g** and oxazolidinylthiazolidines **15a-b** was successfully achieved using both methods. TGA in solution led to yields ranging from 51 to 80%, while TGA anchored to the polymer support afforded the desired thiols in yields ranging from 61 to 93%. Using polymer-supported TGA a notorious 20% yield increase was



Scheme 4. Deprotection reaction using polymer supported TGA as deprotecting agent.

Table 4
Time optimization for the deprotection reaction of **14a** using TG-NCO-SH reagent.

Entry	Time (h)	Yield of 9a (%)[a]
1	2	40
2	6	55
3	24	93

[a] Calculated by HPLC.

Table 5
Recycling of polymer-supported TGA for the deprotection of **14a**.

Entry	Cycle	Resin loading (mmol/g resin)	Yield of 9a (%)[a]
1	1st	0.35	93
2	2nd	0.33	93
3	3rd	0.32	90
4	4th	0.33	89
5	5th	0.32	90
6	6th	0.30	87

[a] Calculated by HPLC.

observed for thioesters **14a** and **14c**, see Table 6, entries 1 and 3 respectively; while similar yields were obtained for all others substrates.

In addition, different acyl side chains like butyryl (**14f**) and phenyl (**14g**) were assayed leading to the desired thiol in moderate to good yields (61 and 76% respectively for solid supported TGA and 58 and 75% respectively for solution TGA).

When TGA-SAc, S-acetyl *n*-propanethiol **16** and S-acetyl thiophenol **17** were used as starting materials, the corresponding free thiols were obtained using both methodologies in good yields, Table 6, entries 10, 11 and 12 respectively. S-acetyl TGA only was assayed in the heterogeneous phase, since in solution is not possible to determine the yield.

These approaches allowed us the chemoselective deprotection of several substrates, keeping the integrity of thiazolidine and oxazolidine scaffolds. The ester hydrolysis was not observed when **14b** or **15b** were used as starting material. In addition, no epimerization of enantiomerically pure bisthiazolidines or oxazolidines was observed.

The resin recycling shows the potential of this methodology regarding yield increasing, waste reduction and shorter time-consuming operation.

3. Conclusion

In summary, this work provides simple and practical methodologies for thiol deprotection in aqueous media. Thioglycolic acid is described as a useful deprotecting agent for thioesters in mild conditions, avoiding oxidation processes and thiazolidine/oxazolidine ring opening.

A solid-supported TGA was also prepared and successfully used for thioester deprotection, affording better yields compared to homogeneous synthesis. Chemical stability and resin recycling were studied, indicating the resin can be reused at least five times without loss of activity.

Overall, the new deprotection methodologies can be applied for the synthesis of labile substrates like analogs of **9a** and different aliphatic or aromatic thiols.

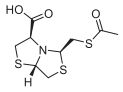
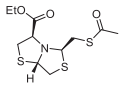
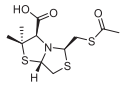
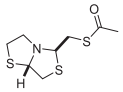
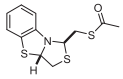
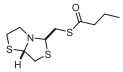
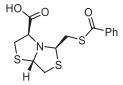
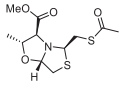
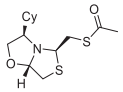
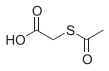
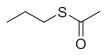
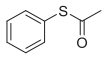
4. Experimental section

4.1. Synthetic procedures

Starting Materials

The following compounds were prepared according to methods

Table 6
Deprotection of thioesters **14a-g**, **15a-b, TGA-SAc, 16** and **17.**

Entry	Starting Material		Product	Yield (%)[a]	
				TG-NCO-SH	TGA in solution
1		14a	9a	93	74
2		**14b**	**9b**	66	56
3		**14c**	**9c**	92	71
4		**14d**	**9d**	79	77
5		**14e**	**9e**	66	51
6		**14f**	**9d**	61	58
7		**14g**	**9a**	76	75
8		**15a**	**10a**	68	69
9		**15b**	**10b**	65	53
10		**TGA-SAc**	**TGA**	87	nd[b]
11		**16**		85	66
12		**17**		53	80

[a] Isolated yields after column chromatography purification.
[b] nd = not determined.

described in literature: **9a** and **9c-d,** [36] **9b** and **9e,** [34] **10a-b.** [35].

Representative Procedure for the Synthesis of S-acetylated bis-thiazolidines **14a-e** and S-acetylated oxazolidinylthiazolidines **15a-b**.

(3R,5R,7aS)-5-((acetylthio)methyl)tetrahydro-2H-thiazolo[4,3-b] thiazole-3-carboxylic acid (**14a**). Into a two-necked flask under nitrogen atmosphere was transferred **9a** (0.5 g, 2.1 mmol) and added dropwise with stirring under ice bath a mixture 1:1 of Ac_2O:Py (2 mL). The mixture was heated to room temperature and stirred for 2 h. Ice frost was added and it was stirred for 1 h. This solution was then poured into Et_2O (30 mL) and extracted with $NaHCO_3$ aq. (2 × 30 mL). The aqueous layer was taken to pH = 2 and extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated to dryness to yield **14a** (0.52 g, 89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.38 (dd, *J* = 8.1, 5.4 Hz, 1H), 4.19 (dd, *J* = 7.1, 2.8 Hz, 1H), 3.61 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.42 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.32 (dd, *J* = 11.5, 7.1 Hz, 1H), 3.24 (dd, *J* = 14.2, 5.5 Hz, 1H), 3.19 (dd, *J* = 14.2, 8.2 Hz, 1H), 3.11 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.40 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.7, 172.3, 73.4, 72.1, 71.8, 39.4, 37.5, 33.6, 30.9; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_9H_{13}NO_3NaS_3$, 301.9955, found 301.9957; $[\alpha]_D^{20}$ − 43.0 (*c* 1.1, EtOAc).

(3R,5R,7aS)-ethyl5-((acetylthio)methyl)tetrahydro-2H-thiazolo [4,3-b]thiazole-3 carboxylate (**14b**). Prepared in an analogous route as described for **14a** starting from **9b** (0.05 g, 0.19 mmol) and purified by column chromatography on flash silica gel (CH_2Cl_2:nHex 2:1) to yield **14b** (0.041 g, 71%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (dd, *J* = 5.4, 3.5 Hz, 1H), 4.29 (t, *J* = 6.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.20 (t, *J* = 5.9 Hz, 1H), 3.58 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.33−3.26 (m, 3H), 3.11−3.06 (m, 2H), 2.35 (s, 3H), 1.31 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.5, 170.5, 74.0, 71.6, 69.9, 61.7, 38.5, 37.8, 34.5, 30.7, 14.3; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{11}H_{17}NO_3NaS_3$, 330.0268, found 330.0268; $[\alpha]_D^{20}$ − 32.4 (*c* 1.59, CH_2Cl_2).

(3R,5R,7aS)-5-((acetylthio)methyl)-2,2-dimethyltetrahydro-2H-thiazolo[4,3-b]thiazole-3-carboxylic acid (**14c**). Prepared in an analogous route as described for **14a** starting from **9c** (0.15 g, 0.57 mmol) and purified by column chromatography on flash silica gel (nHex:EtOAc:AcOH 8:2:0.01) to yield **14c** (0.11 g, 62%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (br, 1H), 5.03 (t, J = 6.0 Hz, 1H), 4.41 (t, J = 7.1 Hz, 1H), 3.75 (s, 1H), 3.49 (dd, J = 11.7, 6,6 Hz, 1H), 3.24 (dd, J = 14.2, 6.6 Hz, 1H), 3.19 (dd, J = 14.1, 7.6 Hz, 1H), 3.04 (dd, J = 11.7, 5.4 Hz, 1H), 2.39 (s, 3H), 1.60 (s, 3H), 1.49 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6, 172.0, 78.5, 72.4, 69.3, 55.1, 40.7, 36.7, 30.7, 28.1, 27.9; HRMS (ESI/Q-TOF) *m/z*: [M + 2Na - H]$^+$ Calcd for $C_{11}H_{16}NO_3Na_2S_3$ 352.0088, found 352.0088; $[\alpha]_D^{20}$ − 38.2 (*c* 1.1, CH_2Cl_2).

(±) ((tetrahydro-2H-thiazolo[4,3-b]thiazol-5-yl*)methyl) ethanethioate* (**14d**). Prepared in an analogous route as described for **14a** starting from **9d** (0.05 g, 0.26 mmol) and purified by column chromatography on flash silica gel (nHex:EtOAc 8:2) to yield **14d** (0.04 g, 65%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) 5.02 (dd, J = 5.1, 3.1 Hz, 1H), 4.21 (t, J = 6.4 Hz, 1H), 3.60−3.48 (m, 2H), 3.25 (dd, J = 13.6, 6.2 Hz, 1H), 3.20−2.99 (m, 5H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6, 75.4, 69.9, 56.9, 38.1, 38.0, 32.1, 30.8; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_8H_{13}NONaS_3$ 258.0057, found 258.0061.

(±) (3,3a-dihydro-1H-benzo[d]thiazolo[4,3-b]thiazol-1-yl*)methanethiol (***14e***)*. Prepared in an analogous route as described for **14a** starting from **9e** (0.5 g, 2.1 mmol) and purified by column chromatography on flash silica gel (nHex:CH_2Cl_2 8:2) to yield **14e** (0.464 g, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.04 (m, 2H), 6.86 (td, J = 7.5, 1.1 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.18 (t, J = 5.2 Hz, 1H), 5.15 (dd, J = 5.4, 3.9 Hz, 1H), 3.32 (dd, J = 13.8, 8.6 Hz, 1H), 3.25 (dd, J = 10.6, 5.3 Hz, 1H), 3.22 (dd, J = 13.8, 5.8 Hz, 1H), 2.92 (t, J = 10.1 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.5, 145.3, 126.4, 124.7, 123.1, 122.2, 110.9, 70.8, 67.3, 40.3, 37.8, 30.8; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{12}H_{13}NONaS_3$, 306.0057, found 306.0056.

(2R,3S,5R,7aS)-methyl 5-((acetylthio)methyl)-2-methyltetrahydro-2H-thiazolo[4,3-b]oxazole-3-carboxylate (**15a**). Prepared in an analogous route as described for **14a** starting from **10a** (0.1 g, 0.4 mmol) and purified by column chromatography on flash silica gel (nHex:EtOAc 9:1) to yield **15a** (0.93 g, 79%)as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (d, J = 4.0 Hz, 1H), 4.29 (dd, J = 8.2, 6.7 Hz, 1H), 4.10 (dq, J = 8.5, 6.0 Hz, 1H), 3.79 (s, 3H), 3.31 (dd, J = 12.9, 4.5 Hz, 1H), 3.22 (d, J = 8.5 Hz, 1H), 3.18 (dd, J = 13.8, 8.3 Hz, 1H), 3.09 (dd, J = 12.9, 0.7 Hz, 1H), 3.05 (dd, J = 13.7, 6.6 Hz, 1H), 2.35 (s, 3H), 1.40 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.2, 171.0, 99.2, 76.4, 74.7, 73.3, 52.3, 37.4, 36.4, 30.6, 18.0; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{11}H_{17}NO_4NaS_2$, 314.0497, found 314.0501; $[\alpha]_D^{20}$ − 61.1 (*c* 0.96, CH_2Cl_2).

S-(((3R,5R,7aS)-3-cyclohexyltetrahydro-2H-thiazolo[4,3-b]oxazol-5-yl*)methyl) ethanethioate* (**15b**). Prepared in an analogous route as described for **14a** starting from **10b** (0.1 g, 0.39 mmol) and purified by column chromatography on flash silica gel (nHex:-EtOAc 9:1) to yield **15b** (0.072 g, 62%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, J = 3.9 Hz, 1H), 4.20 (dd, J = 7.4, 6.9 Hz, 1H), 3.98 (dd, J = 8.4, 6.8 Hz, 1H), 3.52 (dd, J = 8.4, 7.3 Hz, 1H), 3.28 (dd, J = 12.5, 4.3 Hz, 1H), 3.26 (dd, J = 13.8, 6.8 Hz, 1H), 3.07 (dd, J = 12.6, 1.0 Hz, 1H), 2.98 (dd, J = 13.7, 7.7 Hz, 1H), 2.90 (q, J = 7.1 Hz, 1H), 2.35 (s, 3H), 1.97−1.90 (m, 1H), 1.82−1.65 (m, 4H), 1.42−1.33 (m, 1H), 1.31−1.10 (m, 3H), 1.04−0.92 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.5, 99.5, 75.0, 71.2, 68.4, 41.7, 37.2, 37.0, 30.7, 30.6, 29.1, 26.6, 26.4, 26.3; (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{14}H_{23}NO_2NaS_2$ 324.1068, found 324.1068. $[\alpha]_D^{20}$ − 24.4 (*c* 0.96, CH_2Cl_2).

*Synthesis of S-butyryl bisthiazolidine (**14f**)*

(±)((tetrahydro-2H-thiazolo[4,3-b]thiazol-5-yl*)methyl) butanethioate* (**14f**). Into a two-necked flask under nitrogen atmosphere was dissolved **9d** (0.04 g, 0.21 mmol) in CH_2Cl_2 (5 mL) and added dropwise with stirring under ice bath butyryl chloride (0.027 g, 0.25 mmol) and TEA (0.025 g, 0.25 mmol). The mixture was heated to room temperature and stirred for 2 h. Ice frost was added and stirred for 1 h. This mixture was poured into a saturated aqueous solution of NaCl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated to dryness and the crude product was purified by column chromatography on flash silica gel (nHex:EtOAc 9:1) to yield **14f** (0.038 g, 69%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (dd, J = 5.1, 3.1 Hz, 1H), 4.20 (t, J = 6.4 Hz, 1H), 3.58 (dd, J = 11.4, 4.9 Hz, 1H), 3.55−348 (m, 1H), 3.25 (dd, J = 13.6, 6.2 Hz, 1H), 3.20−2.98 (m, 5H), 2.55 (t, J = 7.4 Hz, 2H), 1.70 (sext, J = 7.4, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.3, 75.5, 70.0, 57.0, 46.1, 38.0, 37.6, 32.1, 19.3, 13.6; HRMS (ESI/Q-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{10}H_{17}NONaS_3$ 286.0370, found 286.0370.

*Synthesis of S-benzoyl bisthiazolidine **14g***

(3R,5R,7aS)-5-((benzoylthio)methyl)tetrahydro-2H-thiazolo[4,3-b]thiazole-3-carboxylic acid (**14f**). Prepared in an analogous route as described for **14f** starting from **9a** (0.35 g, 1.5 mmol) and benzoyl chloride (0.23 g, 1.6 mmol), purified by column chromatography on flash silica gel (CH_2Cl_2:EtOAc:AcOH 9:1:0.01) to yield **14g** (0.36 g, 71%) as a white powder: MP = 75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.96 (m, 2H), 7.64−7.59 (m, 1H), 7.50−7.45 (m, 2H), 5.12 (dd, J = 6.0, 3.9 Hz, 1H), 4.50 (dd, J = 8.3, 5.0 Hz, 1H), 4.23 (dd, J = 7.1, 2.6 Hz, 1H), 3.67 (dd, J = 12.0, 6.0 Hz, 1H), 3.46 (dd, J = 14.2, 5.0 Hz, 1H), 3.44 (dd, J = 11.6, 2.4 Hz, 1H), 3.37 (dd, J = 14.1, 8.3 Hz, 1H), 3.32 (dd, J = 11.4, 7.1 Hz, 1H), 3.14 (dd, J = 12.0, 3.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.7, 171.7, 136.4, 134.3, 129.0, 127.7, 73.5, 72.3, 72.1, 39.5, 37.4, 33.5; HRMS (ESI/Q-TOF) *m/z*: [M + 2Na - H]$^+$ Calcd for $C_{14}H_{14}NO_3Na_2S_3$ 385.9931, found 385.9931; $[\alpha]_D^{20}$ − 27.8 (*c* 1.72, CH_2Cl_2).

5. S-acetyl bisthiazolidines deprotection

*Deprotection of **14a** using $NH_2OH{\cdot}HCl$* (Table 2, Entry 2): Into a two-necked flask, under nitrogen atmosphere, was dissolved **14a** (0.1 g, 0.36 mmol) in dry MeOH (4 mL) and added under ice bath $NH_2OH{\cdot}HCl$ (0.097 g, 1.4 mmol) and TEA (0.21 g, 2.1 mmol). The reaction mixture was heated to room temperature and stirred for 15 min. It was poured into HCl 5% and extracted with EtOAc (3 × 30 mL). The combined organic extracts were concentrated to dryness and the crude product was purified by column chromatography on flash silica gel (nHex/EtOAc/AcOH 7:3:0.01) to yield **9a** (0.027 g, 33%).

*Deprotection of **14a** using TGA* (Table 3, entry 1): Into a two-necked flask was dissolved **14a** (0.05 g, 0.18 mmol) in MeOH (1 mL) and added BP at pH 8 (19 mL) and TGA (0.025 mL, 0.36 mmol). The reaction mixture was stirred for 30 min at room temperature. It was poured into HCl 5% and extracted with EtOAc (3 × 30 mL). The combined organic extracts were concentrated to dryness and the crude product was purified by column chromatography on flash silica gel (*n*Hex/EtOAc/AcOH 7:3:0.01) to yield **9a** (0.032 g, 75%).

Deprotection of **14a** using *n*-propanethiol, β-Mercaptoethanol, Thiophenol, 2-NH_2-4-Cl-thiophenol, Dithiothreitol (DTT) and Glutathione was carried out using the same method as described for TGA.

5.1. Preparation of polymer-supported exchange thiol (TG-NCO-SH)

O-(2-Aminoethyl)polyethylene glycol resin (0.1 g, 0.4 mmol/g, 1% DVB cross-linked, 100–200 mesh) was added to a syringe vessel and swollen in DMF (2 mL, 30 min). It was added a solution of 2-(acetylthio)acetic acid (0.026 g, 0.19 mmol), HBTU (0.073 g, 0.19 mmol) and DIPEA (0.054 mL, 0.29 mmol) in DMF (0.5 mL). The resin was shaken for 2 h. Reaction completion was monitored by Kaiser test. When a negative Kaiser test is obtained (2 cycles) the resin is filtered and washed with DMF (0.5 min x3). Finally, unreacted sites are capped by treatment with a solution of Ac_2O (300 μL), DIPEA (150 μL) in DMF (2.5 mL) for 15 min. After filtering, resin was washed with DMF (5 × 0.5 min). The resin was treated with a mixture of 2-mercaptoethanol (0.1 mL) and DIPEA (0.1 mL) in DMF (1.8 mL) and shaken under nitrogen atmosphere (3 × 15 min). After filtering the resin was washed with DMF (7 × 0.5min), and thiol loading was calculated by Ellman's method.

5.2. Ninhydrin test

Blank: Into a 10 × 75-mm test tube was weighed an aliquot corresponding to 3 mg of dry resin TG-HL-NH_2. It was added a solution of phenol in absolute ethanol (42.5 mM, 100 μL) a solution of ninhydrin in absolute ethanol (280 mM, 100 μL) and a solution of NaCN in water (2 mM, 100 μL), mixed and placed in a heating block preadjusted to 100 °C. The color of this solution is dark blue.

Sample: Into a 10 × 75-mm test tube was weighed an aliquot corresponding to 3 mg of dry resin after coupling reaction. It was added a solution of phenol in absolute ethanol (42.5 mM, 100 μL) a solution of ninhydrin in absolute ethanol (280 mM, 100 μL) and a solution of NaCN in water (2 mM, 100 μL), mixed and placed in a heating block preadjusted to 100 °C. Color did not develop after 10 min.

Thiol quantification: Ellman's method: Into a 5 mL volumetric flask was accurately weighed an aliquot corresponding to 3 mg of dry resin. It was added THF (1 mL), a solution of Ellman's reagent in MeOH (5.0×10^{-3} M in methanol, 1 mL), and DIPEA (5 μL). The flask was shaken on an orbital shaker for 30 min and diluted to 5.0 ml with methanol. Then, the solution was diluted (1/10) and the absorbance at 412 nm ($\varepsilon = 13600\ M^{-1}cm^{-1}$) was measured against a blank reference (A = 0.279, 0.354 meq/g resin).

Time optimization of deprotection reaction using 14a as starting material and TG-NCO-SH resin as deprotect agent (Table 4): A solution of **14a** (0.004 g, 0.015 mmol) in MeOH (0.1 mL) and degassed BP pH 8 (0.4 mL) was added to the polymer-supported catalyst (TG-NCO-SH, 0.09 g, 0.03 mmol) and stirred under nitrogen atmosphere at room temperature. At suitable intervals (2, 6 and 24 h) the filtrate was collected, diluted and analyzed by analytical HPLC.

TG-NCO-SH-catalyzed deprotection of 14a (Scale up): A solution of **14a** (0.0227 g, 0.081 mmol) in MeOH (0.5 mL) and degassed BP pH 8 (1.0 mL) was added to the polymer-supported catalyst (TG-NCO-SH, 0.3961 g, 0.162 mmol) and stirred for 24 h at room temperature under nitrogen atmosphere. Then, the polymer was filtered and washed with MeOH. The organic layer was dried over Na_2SO_4 and evaporated. The mixture was poured into HCl 5% and extracted with EtOAc (3 × 30 mL). The solvent was removed under reduced pressure to give compound **9a** (0.0181 g, 94%).

Deprotection of **14b-g** and **15a-b** using TG-NCO-SH as deprotect agent was carried out using the same approach as described for **14a**.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132335.

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