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S-4-Methoxytrityl mercapto acids: synthesis and application

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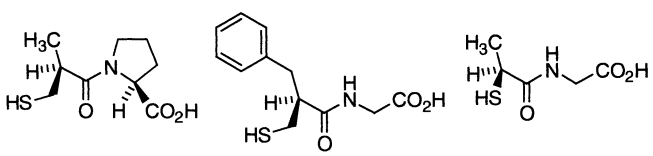
Abstract—4-Methoxytrityl (Mmt)-mercapto acids were obtained either by the reaction of mercapto acids with Mmt-chloride or by the reaction of halo acids with Mmt-thiol. The derivatives obtained were used in the solid-phase synthesis of small libraries of mercaptoacylamino acids and mercaptoacyl peptides. The removal of the Mmt-group was performed by treatment with trifluoroacetic acid (TFA) in dichloromethane (DCM) using triethylsilane (TES) as scavenger. © 2001 Elsevier Science Ltd. All rights reserved.

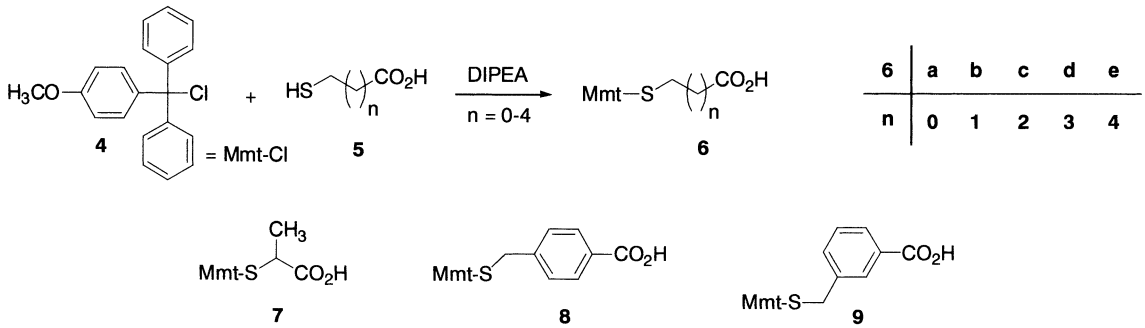
Mercapto acids are constituents of important drugs such as the enzyme inhibitors captopril **1**[1,2] and thiorphane **2**[3,4] and the radio- and chemoprotective agent tiopronine **3**. In addition, mercaptoacyl dipeptides are strong dual peptidase inhibitors.[5] For the development of new drugs using solid-phase combinatorial methods, suitably *S*-protected mercapto acid derivatives are required.



1 **2** **3**

The trityl (Trt) group is an effective protecting group for mercaptans and especially for the thiol-group of cysteine.[6] The synthesis of Trt-mercaptans can be performed by treatment of mercapto-compounds with Trt-chloride or by the reaction of alkyl halides with Trt-thiol.[7,8] The removal of the *S*-Trt-group requires treatment with concentrated TFA and is reversible. In contrast, the *S*-Mmt-group is very acid-labile and can be removed by 1% TFA selectively in the presence of protecting groups of the *tert*-butyl-type.[9] To obtain very acid labile protected derivatives of mercapto acids, we synthesised the corresponding *S*-Mmt-derivatives.[10]

Thus, we treated the mercapto acids **5** with Mmt-chloride **4** and 90% of the calculated equimolar amount of diisopropylethylamine (DIPEA) in DCM/dimethylformamide (DMF) (1:1) for 1 h at rt (Scheme 1). Under these conditions no concurrent tritylation of the carboxy group was observed. We obtained the *S*-Mmt protected linear chain acids **6** in 75–85% yield and >98% purity, D,L-thiolactic acid **7** and mercaptomethylbenzoic acids **8** and **9** in 75–80% yield and >97% purity. For the preparation of the *S*-Mmt butyric acid the corresponding sodium salt was used.



Scheme 1.

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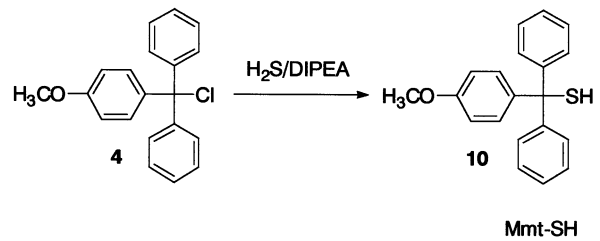
Mercapto acids are of limited commercial availability and they are usually prepared from the corresponding halo acids. To avoid the reaction step required for the conversion of the halo to the corresponding mercapto acid, we reacted halo acids or esters with Mmt-thiol **10**. This was obtained as a crystalline compound (mp: 98–101°C) in 74% yield by the reaction of Mmt-chloride with hydrogen sulfide in DCM/DMF (1:1) for 3 h at rt (Scheme 2).

For the preparation of the *S*-protected mercapto acids we reacted halo acids or esters **11** with Mmt-thiol and excess DIPEA in DMF for 4 h at rt (Scheme 3). No by-products were detected in the reaction mixtures by TLC and HPLC analysis. The *S*-Mmt esters were hydrolysed with aqueous NaOH in dioxane/H_2O (1:1) for 2 h at rt, to yield the corresponding Mmt-mercapto acids. Extractive work up of the reaction mixtures gave **6** as crystalline compounds in 75–85% yield and >96% purity. Compounds **7**, **8** and **9** were also obtained in crystalline form by the reaction of Mmt-thiol **10** with the corresponding halo acids in high yield and >98% purity.

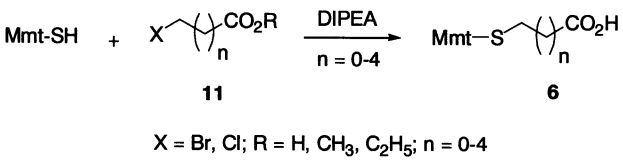
To examine the utility of the Mmt-derivatives **6–9** in solid-phase synthesis we coupled them with small amino acid libraries esterified on 2-chlorotrityl resin.[11] The amino acids were chosen to enable the separation of the products by semipreparative HPLC. As an example, the mixture of the Mmt-protected mercaptopropionyl (Mpr)-amino acid library **14** was prepared by coupling a threefold molar excess of Mmt-Mpr-OH **6b** to the resin-bound library **12** using diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) as the condensing agent (Scheme 4). The reaction was complete in 90 min at rt as determined by the Kaiser test, indicating a similar coupling behaviour of *S*-Mmt-mercapto acids and *N*-protected amino acids. The library **14** was cleaved quantitatively from the resin by treating **13** with acetic acid (AcOH)/trifluoroethanol (TFE)/DCM (1:2:7) for 15 min at rt. This left the *S*-Mmt protection unaffected. The product mixture obtained was analysed by RP-HPLC (Fig. 1). The individual components were separated by semipreparative HPLC and were identified by ES-MS.

In contrast to the treatment with acetic acid, the *S*-Mmt-function is very sensitive towards TFA. Thus treatment of **6–9** with 1 and 5% TFA in DCM/TES (95:5) for 45 and 5 min, respectively, at rt, effected complete cleavage of the Mmt-group.

In a further application Mmt-mercaptobenzoic acid (Mba) **9** was coupled with the resin bound 95–101 fragment **15** of prothymosin α (ProTa) (Scheme 5). The *S*-Mmt protected peptide **17** was obtained by treating **16** with AcOH/TFE/DCM (1:2:7) for 15 min.



Scheme 2.



Scheme 3.

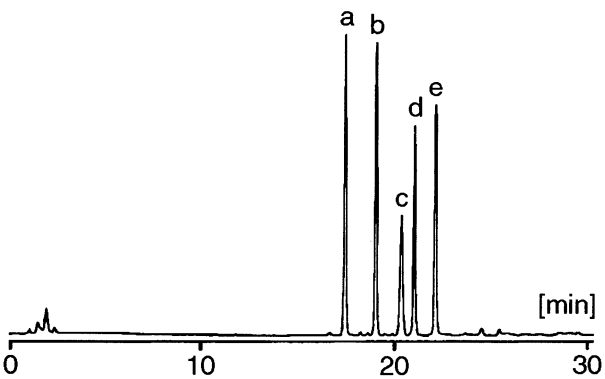
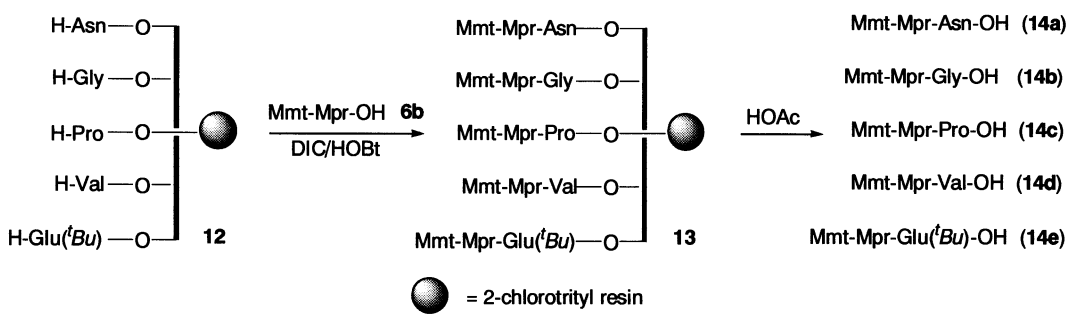
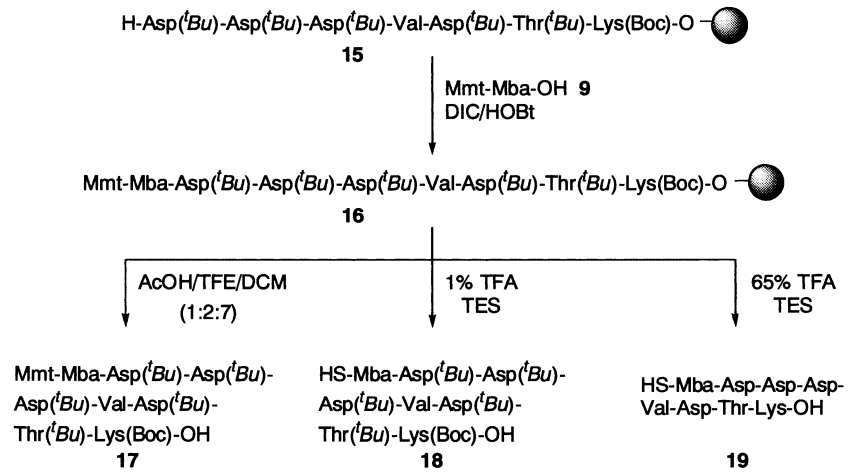


Figure 1. Analytical HPLC of the crude library of **14a–e**; Column: Lichrospher RP-8, 5 μm; 4×150 mm; gradient from 20 to 100% B within 30 min; eluant A: 0.1% TFA in water, eluant B: 0.1% TFA in acetonitrile; flow rate 1 ml/min; detection at 254 nm.



Scheme 4.



Scheme 5.

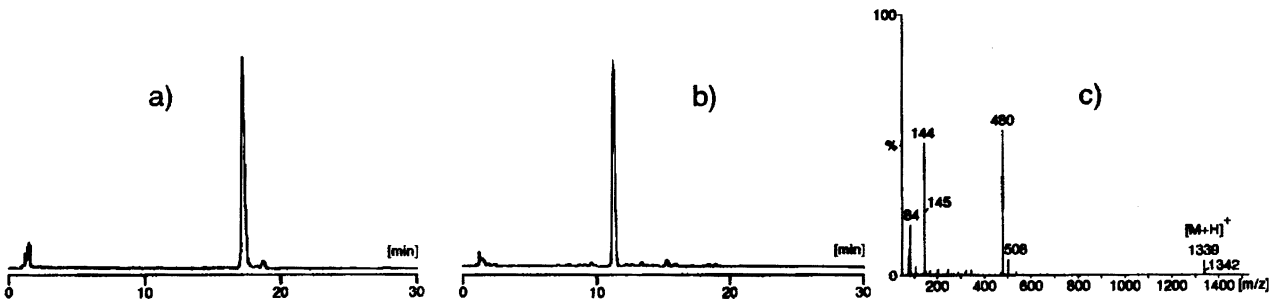


Figure 2. (a) Analytical HPLC of **17** in DMF; Column: Nucleosil C8, 5 μm; 4×125 mm; gradient: from 50 to 100% acetonitrile in water within 30 min; flow rate 1 ml/min; detection at 254 nm. (b) Analytical HPLC of **18** in DMF (conditions as in Fig. 2a). (c) ES-MS analysis of purified **18** at 30 V.

Cleavage with 1% TFA in DCM/TES (95:5) gave the selectively *S*-deprotected peptide **18**, while cleavage with 65% TFA in DCM/TES (95:5) for 1 h at rt, gave the fully deprotected peptide **19**. Peptides **17**–**19** were precipitated from ether and their purity was detected by HPLC analysis. Their correct mass was identified by ES-MS (Fig. 2).

Acknowledgements

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