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Resin-bound mercapto acids: synthesis and application

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Abstract—Mercapto acids were attached through their thiol group onto 2-chlorotrityl (Clt)-, trityl (Trt)-, 4-methyltrityl (Mtt)-, 4-methoxytrityl (Mmt)- and 4,4′-dimethoxytrityl (Dmt)-resins. The new resins were used in the solid-phase synthesis of small mercaptoacylamino alcohols. Cleavage from the resins was performed by treatment with trifluoroacetic acid (TFA) solutions in dichloromethane (DCM) using triethylsilane (TES) as scavenger.

Mercaptoacyl aminoacids are inhibitors of several metallopeptidases, such as the antihypertensive captopril **1**[1,2] and the analgesic thiorphane **2**[3,4] (Fig. 1). In addition, mercaptoacyl dipeptides are strong dual peptidase inhibitors.[5–7] In order to synthesize new lead structures using solid-phase combinatorial methods, suitably resin-bound mercapto acids are required.

The Trt- and Mmt-groups, are useful protecting groups for the thiol-group of cysteine.[8] Therefore, we applied resins of the trityl-type **3**,[9–11] for the attachment of mercapto acids[12] through their thiol group. Thus, a two-fold molar excess of **4** and less than an equimolar amount of diisopropylethylamine (DIPEA) was left to react with resins **3** for 0.5–2 h at rt in DCM/dimethylformamide (DMF) (1:1) (Scheme 1). Under these conditions the attachment of **4** through their carboxy group is not possible. To ensure that thiols **4** were exclusively bound to the various resins by their thiol function, **5** were treated with a mixture of acetic acid (AcOH)/TFE/DCM (1:2:7) for 15 min at rt. Under these conditions the resin-bound carboxy group is cleaved quantitatively, even in the case of the most acid stable resin **5e**. Unreacted remaining trityl chlorides were converted to the corresponding inert trityl–methyl ethers, by washing resins **5** with methanol (MeOH)/DIPEA/DCM (15:5:80). The loading of the resins obtained was determined by sulfur analysis. We observed highest attachment rates in the case of **5a**–**b**. Thus, resins **5a**–**b** were obtained within 30 min with a loading of 0.7–0.8 mmol **4**/g. In contrast, **5e** gave at the same time resins with a loading of 0.4–0.6 mmol **4**/g. Besides resin-bound linear mercapto acids **5**, we obtained in excellent yield the sterically hindered thiolactic acid **6** and the *m*- and *p*-mercaptomethyl benzoic acids **7**, **8**.

The cleavage of the mercapto acids from the various resins was performed by treatment with TFA solutions in DCM/TES (97:3). In general the acid sensitivity of the mercapto–resin bond seems to be independent of the bound mercapto acids. The acid sensitivity of the resin-bound mercapto acids increases considerably from **5e** to **5a**. Thus, complete cleavage of the mercapto acids from the resins **5a**–**e** was effected by 4×3 min treatment

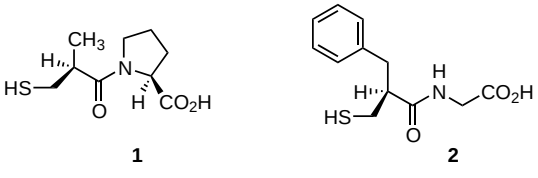
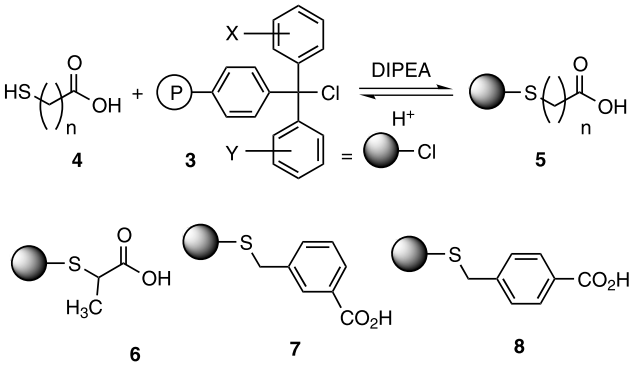


Figure 1.



3; X,Y = 4-CH_3O, 4-CH_3O (**a**), 4-CH_3O, H (**b**), 4-CH_3, H (**c**), H, H (**d**), 2-Cl, H (**e**), n = 1-5

Scheme 1.

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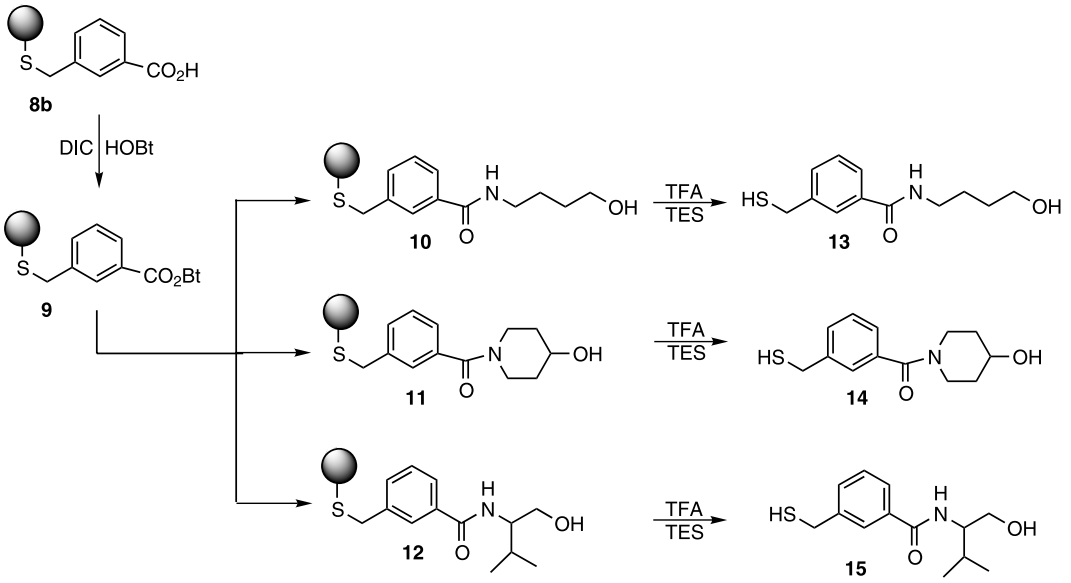
with 0.5, 1.1, 10, 30 and 65% TFA, respectively in DCM/TES (97:3).

The utility of resin-bound mercapto acids in solid-phase synthesis was investigated during their coupling with amino components. Thus, **5–8** were converted to the corresponding benzotriazolyl esters, by treatment with excess diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) in tetrahydrofuran (THF) for 4 h at rt. The resin-bound mercapto acid benzotriazolyl esters obtained were reacted with a three-fold molar excess of amino acid esters and aminoalcohols (linear, cyclic and derived from amino acids). In one example, **8b** was converted to the active ester **9** and reacted subsequently in DMF, for 1 h at rt with aminobutanol, 4-hydroxypiperidine and valinol, to yield the resin-bound mercaptoacylamino alcohols **10–12** (Scheme 2). Treatment with 1.1% TFA in DCM/TES (97:3) for 4×3 min, released the crude alcohols **13–15** in 89, 94 and 92% yields and 94, 92 and 94% purity, respectively, according to HPLC analysis (Fig. 2a–c). Their correct molecular weight was determined by ES–MS (Fig. 2d–f).

The conversion of the resin-bound mercapto acids to the corresponding benzotriazolyl esters and mercaptoacylamino alcohols were directly monitored by FT-IR analysis. As an example, the conversion of **8b** to the benzotriazolyl ester **9** was observed by the complete



Scheme 2.

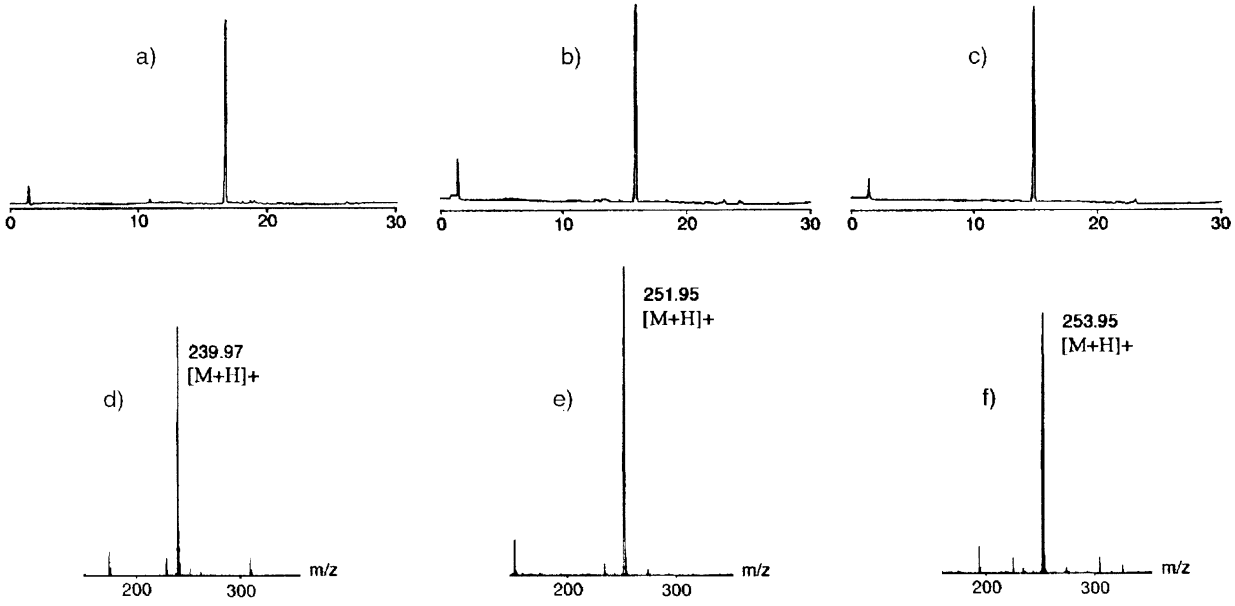


Figure 2. Analytical HPLC of crude **13** (a), **14** (b) and **15** (c); column: Lichrospher RP-8, 5 μm; 4×150 mm; gradient: from 20 to 100% B acetonitrile in water within 30 min; flow rate 1 ml/min; detection at 254 nm; ES–MS at 30 eV of purified **13** (d), **14** (e) and **15** (f).

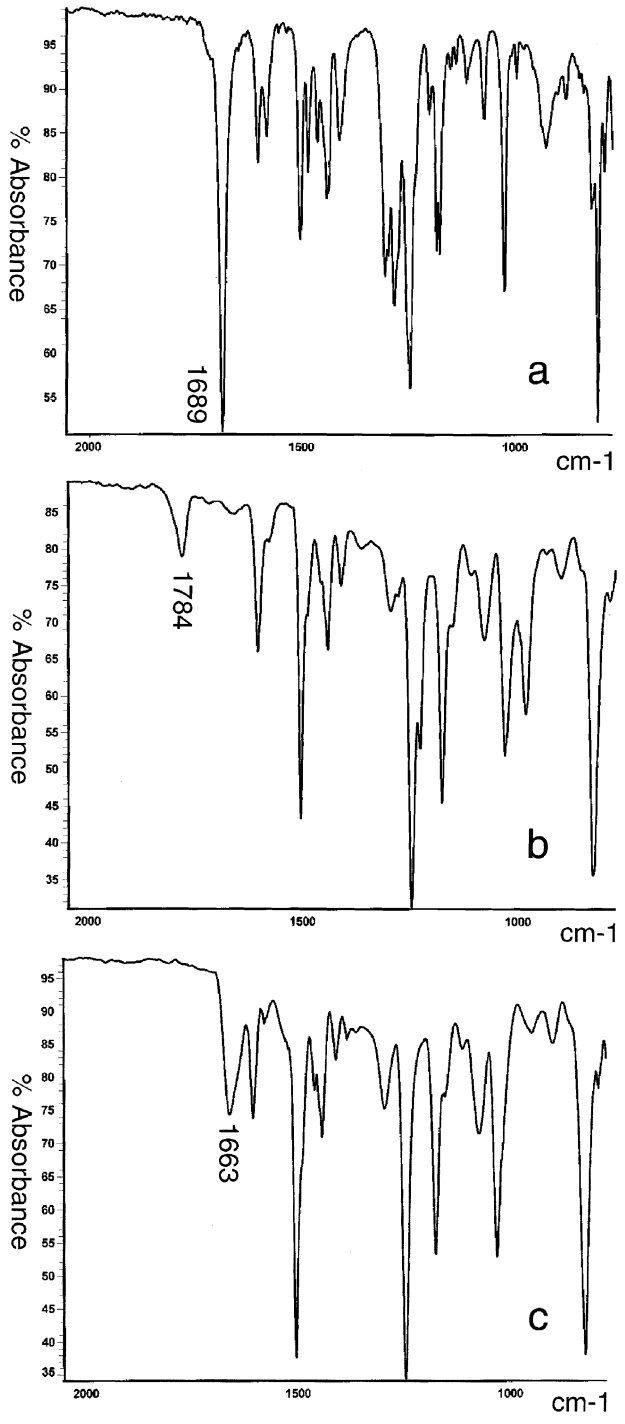


Figure 3. FT-IR analysis of **8b** (a), **9** (b) and **12** (c).

disappearance of the carboxy carbonyl frequency at 1689 cm^{-1} and the appearance of an ester carbonyl frequency at 1784 cm^{-1} (Fig. 3a–b). The second reaction is the nucleophilic replacement of the hydroxybenzotriazolyl group of **9** by the amino group of valinol. The success of this step is shown by the appearance of the amide carbonyl band at 1663 cm^{-1}. The conversion was complete as seen by the disappearance of the ester carbonyl band at 1784 cm^{-1} (Fig. 3b–c).

Acknowledgements

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