Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7321-7324, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01778-4

The Use of Thioesters in Solid Phase Organic Synthesis

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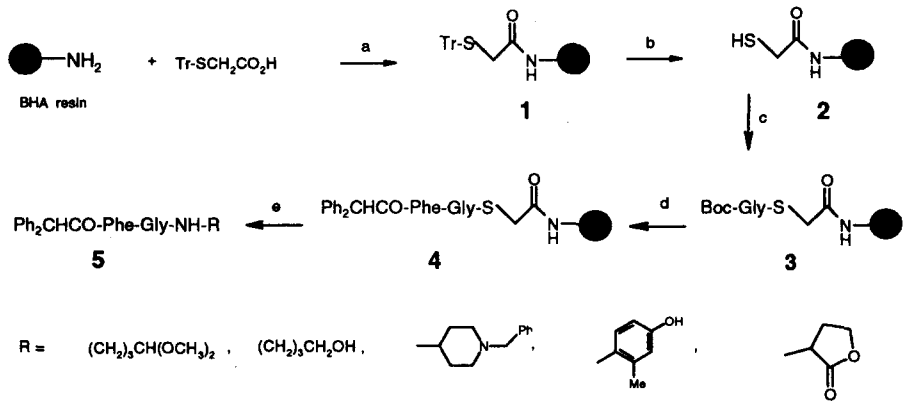
Abstract: Mercaptan-resin linkers are used for the synthesis of C-terminal thioesters which are then cleaved with alcohols, amines and organometallic reagents to generate esters, amides, ketones, aldehydes and alcohols as the final products of solid phase synthesis. © 1997 Elsevier Science Ltd.

In the course of solid phase synthesis of compound libraries, it is sometime desirable that the final cleavage reaction from the solid support is chosen in a way that will induce additional structural diversity in the end product. In this communication, we would like to report the use of thioesters linkers[1] as "C-terminal" activated carboxyl groups that can be cleaved with alcohols, amines and organometallic reagents to generate esters, amides,[2] ketones,[3] aldehydes and alcohols[4] as final products.

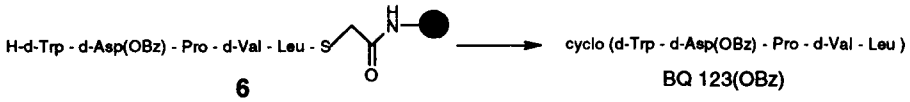
A typical synthesis of a thioester dipeptide **4** and its reaction with primary amines to generate C- terminal amides **5** is illustrated in Scheme 1.[5] The molarity of the mercaptan linker **2** was determined from the amount of triphenylmethane produced in step b and was usually 95% of the molarity of the benzhydrylamine resin. In an exception to the general rule[1] for the preparation of thioesters on solid support where thioester linkers were prepared in solution prior to resin loading, compound **3** was prepared by direct esterification of the mercaptan linker **2**. The dipeptide **4** was subsequently synthesized from **3** using a Boc-synthetic protocol.[1] When primary alcohols such as ethanol were used as the solvent in the amine cleavage reaction, considerable amounts of the ester products were produced. In isopropanol or non hydroxylic solvents such as dioxane, the amides **5** were produced in essentially analytically pure form and in 70-80% yields. The isolation of the amides **5** was carried out by filtering and washing the resin, evaporating of the filtrates, extracting the residue with ethyl acetate and 1N hydrochloric acid and then drying and evaporating the ethyl acetate layer.[6]

Scheme 1



Reagents and conditions: (a)BHA resin (0.86 mmole/gr), Ts-CH_2COOH (4 eq.), DCC (2 eq.), DMF/DCM(1:2 v/v), 24 hrs; (b) TFA/DCM/Et_3SiH (5:5:1, v/v); (c) Boc-Gly-OH (4 eq.), DCC/DMAP (1:1, 4 eq.), DCM, 24 hrs; (d) TFA/DCM (1:1) then Ph_2CHCO-Phe-OH (4 eq.), HBTU/HOBT (1:1, 4 eq.), DIEA (12 eq.); (e) R-NH_2 (3 eq.), i-propanol, 75°C, 24 hrs.

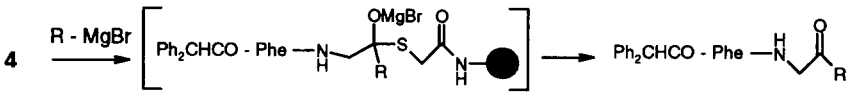
We have subsequently tested this facile primary amine reaction of C-terminal thioesters in the synthesis of cyclic peptides from linear peptide intermediates on solid support. For this purpose we have chosen as target the endothelin receptor antagonist, BQ 123.[7] A Boc-synthetic protocol was used for the synthesis of the linear peptide **6**. The cyclic peptide was then obtained analytically pure in 50% yield by heating **6** in DMF or dioxane at 75°C for 24 hours.

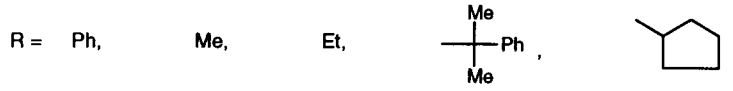


C-terminal aldehydes or ketones are often desirable functionalities in the synthesis of cysteine[8] or serine[8] protease inhibitors. Within the context of combinatorial synthesis, the activated C-terminal carboxyl groups of thioesters on solid support were therefore attractive substrates for the generation of this class of compounds. We have found that thioesters such as **4** show a remarkable selectivity to Grignard reagents. Scheme 2 shows the results of the reaction of **4** with a variety of commercially available Grignard reagents (Aldrich). The Grignard reactions were carried out in THF using 5 to 10 equivalents of the Grignard reagent at room temperature. At the end of the reaction the resin was first washed twice with dry THF. The intermediate alkoxy metal complex **7** remaining on the resin was then decomposed with a proton donor such as aq. ammonium chloride or formic acid in THF, thus releasing pure ketone uncontaminated from byproducts in the filtrates. Ketones **8** were obtained

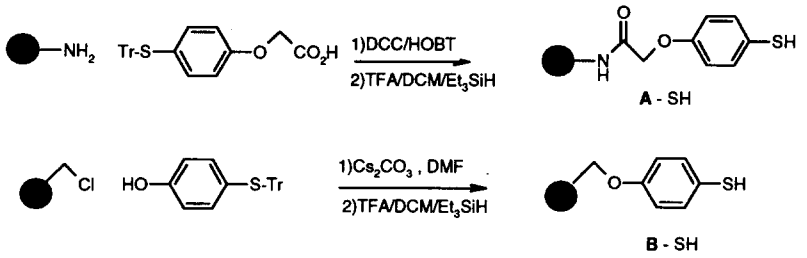
essentially analytically pure in 50 to 60% yields. Remarkably, no tertiary alcohol products were detected in the original washings prior to the release of the end product from the resin.

Scheme 2

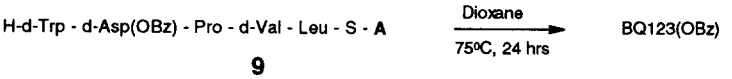


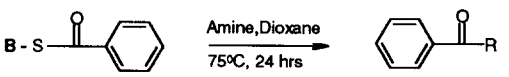


Secondary amines reacted sluggishly with **4** requiring prolonged reaction periods and leading to impure products. It was therefore desirable to have more reactive thioesters for the synthesis of amides from hindered or weak nucleophilic amines.[9] We investigated the use of the mercapto-linkers **A** - SH and **B** - SH which were



expected to form more reactive thioesters than those derived from **2**. Thus, the linear amide **9** was smoothly cyclized to BQ123(OBz) and the benzoyl thioester **10** gave the amides **11** in good (60-70%) yields. These





R = HN -Phe -(OMe), Pro-OMe , $HNCH_2CH(OCH_3)_2$

reactions lead us to believe that it might be possible to carry out coupling of peptide fragments on solid phase. Further results on this investigation will be reported.

In synopsis, this work describes the use of novel mercaptan linkers that are used in the construction of organic molecules attached to the solid support via a thioester linker. These activated esters are then cleaved with nucleophiles to generate a variety of "C-terminal" functionalized compounds that are of particular interest in medicinal chemistry.

Acknowledgments: We thank Leonard Hargiss and James Munson for MS data.

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5. Abbreviations: BHA = Benzhydrylamine; Tr = Trityl; HBTU = O-Benzotriazole-N,N,N',N'-tetramethyl-uronium hexafluorophosphate; HOBT = 1-Hydroxybenzotriazole; DMF = N,N-Dimethyformamide; TFA = Trifluoroacetic acid; DCM = Dichloromethane; DMAP = 4-Dimethyaminopyridine; DIEA = Diisopropylethylamine.
6. Products were characterized by LC/MS and amino acid or elemental (C, H, N) analysis.
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(*Received in USA* 25 *July* 1997; *revised* 18 *August* 1997; *accepted* 19 *August* 1997)