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Cyclo-release synthesis of cyclic disulfides on solid phase

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Abstract

A method to synthesise on solid phase cyclic disulfides by a cyclo-release reaction triggered by a dimethyl(thio)sulfonium moiety is described. © 2000 Published by Elsevier Science Ltd.

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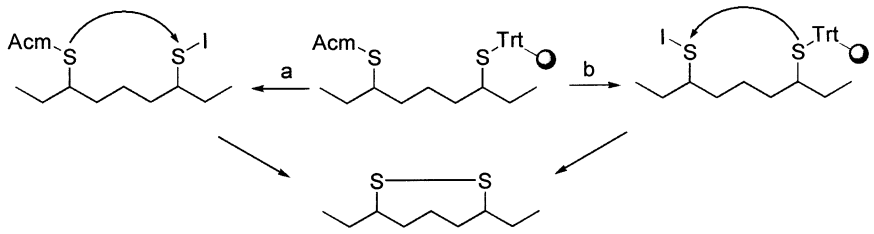
The usual strategy to synthesise cyclic disulfides on solid phase is derived from peptide synthesis. The peptide chain is prepared on the resin with the two sulfur atoms protected. The disulfide bond formation could be performed on the resin or in solution after cleavage with either protected or unprotected thiols.[1]

In solid phase peptide synthesis, in order to avoid racemisation the chain is usually elongated from the nitrogen atom ($C \rightarrow N$ strategy).[2] For peptidomimetics synthesis, where the risk of racemisation is different, it might be interesting to link directly the thiol on the resin in order to have more flexibility in chain elongation. Such a strategy has already been described for peptide synthesis using a trityl linker: the disulfide was formed by oxidative cleavage using iodine. The reaction mechanism was solvent dependent: DMF led to a cyclo-release of the cyclic disulfide, while a mixture of methanol and chloroform led to cleavage of the peptide from the resin and the cyclisation occurred in solution[3] (Scheme 1).



Scheme 1. Reagents and conditions: (a) I_2, $CHCl_3/CH_3OH$; (b) I_2, DMF

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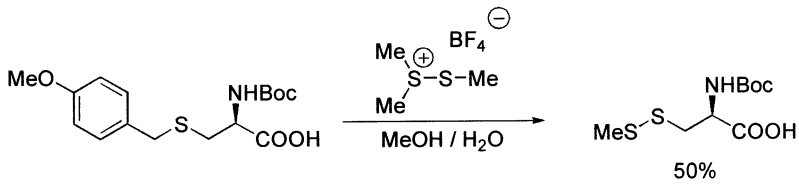
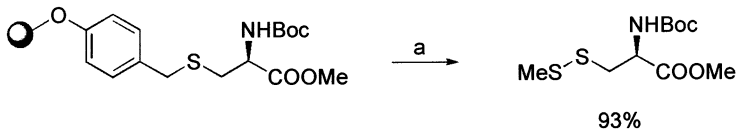
In this paper we describe a new method based on the cyclo-release concept with a less hindered, and less-acid sensitive, linker. The strategy was triggered by a work published by Chmielewski and co-workers[4] who described the formation of disulfide bond from a *p*-methoxybenzylthioether using dimethyl(methylthio)sulfonium tetrafluoroborate (Scheme 2).



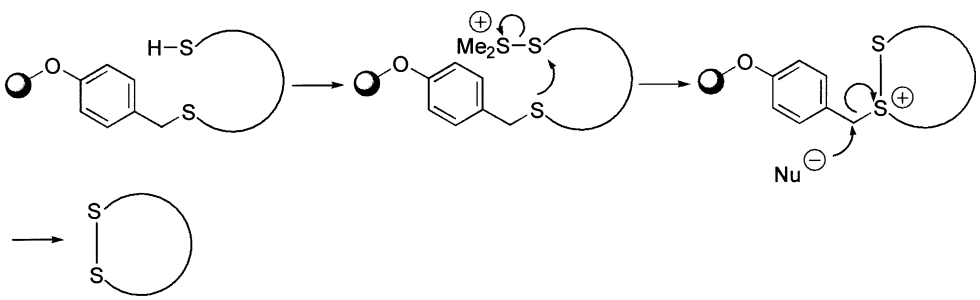
Scheme 2.

Since there is a strong analogy between a Wang resin and a *p*-methoxybenzyl group we carried out the above reaction on a solid phase support with an excellent yield.[10] Furthermore this experiment showed that an excess of dimethyl(methylthio)sulfonium tetrafluoroborate had no effect on the reaction product (Scheme 3).



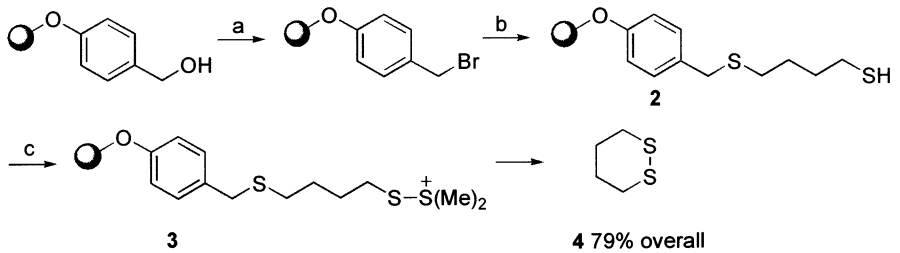
Scheme 3. Reagents and conditions: (a) $(CH_3)_2S{+}SCH_3BF_4{-}$ (2 equiv.), DMF (0.01 M), rt, 24 h

Considering the reaction mechanism, we reasoned that if the dimethyl(thio)sulfonium moiety is included in the molecule hooked on the resin, a cyclisation reaction might occur by a cyclo-release mechanism. Since the reaction conditions in a resin core can be equated to high dilution conditions,[5] the cyclic reaction must be favoured and by-products coming from intermolecular reactions should remain on the resin (cross linking reaction) (Scheme 4).



Scheme 4.

1,4-Butanedithiol **1** was selected as the model substrate. Reaction of an excess of **1** with a bromo-Wang[6] resin afforded the polymer-bound thiol **2**. The dimethyl(thio)sulfonium **3** was prepared using the complex of *N*-chlorosuccinimide and dimethylsulfide (NCS/DMF).[7,8] It cyclised spontaneously at room temperature to the desired 1,2-dithiane **4** in excellent yield (Scheme 5).[10]



Scheme 5. Reagents and conditions : (a) NBS (5 equiv.), CH_3SCH_3 (5.5 equiv.), CH_2Cl_2 ($c=0.21$ M), 0°C, 2 h, 30 min; (b) $HSCH_2(CH_2)_2CH_2SH$ (10 equiv.), DBU (4 equiv.), toluene ($c_{thiol}=0.43$ M), rt, 10 h; (c) NCS (4 equiv.), CH_3SCH_3 (5 equiv.), CH_2Cl_2 ($c_{NCS}=0.08$ M), 0°C, 10 min; then resin is added, 0°C, 2 h, then 2 h at rt

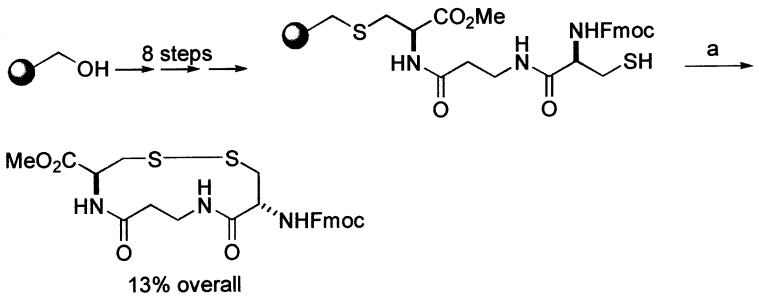
Using the same reaction conditions we were able to prepare cyclic aliphatic disulfides having up to a 14-membered ring.[9] Analysis of the reaction filtrate showed only the cyclic disulfide and we were unable to detect either oligomeric products or larger rings (Table 1).

Table 1

Ringsize	6	7	9	11	12	14
Yield (%)[a,10]	79	75	29	46	41	61

[a] Yields are calculated from the starting Wang resin on purified products (flash chromatography on silica gel with a 9/1 mixture of petroleum ether and acetone).

Since we intend to use this strategy to synthesise peptidomimetics with a disulfide bridge, we needed to test this reaction in the presence of amide bonds. Thus, the above method was used to prepare a cyclic disulfide including two cysteines and a β-alanine[10] (Scheme 6).



Scheme 6. Reagents and conditions: (a) NCS (4 equiv.), CH_3SCH_3 (5 equiv.), CH_2Cl_2 ($c_{NCS}=0.1$ M), 0°C, 4 h

The complex NCS/DMS is a very mild reagent, compatible with a large number of protective groups, which promotes on solid phase the formation of a cyclic disulfide from a sulfide and a thiol. Consequently, this methodology is now used in our laboratories to synthesise libraries of cyclic peptido mimetics with a single disulfide bridge.

Acknowledgements

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9. The chlorodimethylsulfonium hexachloroantimonate can be used instead of the NCS/dimethylsulfide complex. However the yields of isolated aliphatic disulfides are lower; see: Neidlein, B.; Stackebrandt, B. *Liebigs Ann. Chem.* **1977**, 914–923.
10. Experiments are carried on 400 mg of Wang resin with a 1.05 meq/g loading. All products gave satisfactory analytical data (^{13}C and ^{1}H NMR, LC/MS).