

Synthesis of 1,3-Dimercaptopropylarsen-boc-cysteine-O-Bzl

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Introduction: As a first molecule, suitable for labelling with nca arsenic isotopes as delivered from the new $^{72}\text{Se}/^{72}\text{As}$ -generator-system, based on solid-phase extraction [1] or from the As/Ge-separation as described in [2], the amino acid cysteine was chosen.

As cysteine is SH-functionalized it will have a high affinity to arsenic and will allow stable covalent bonds. As an amino acid, cysteine is involved in peptide biosynthesis. The protein synthesis rate increases in tumor growth. It should be possible to use ^{72}As -cystein for the diagnosis of tumor processes with long biological half-lives via PET or an ^{77}As -cystein for therapeutics of some tumor sorts. This work describes the synthesis of the cold standard.

Experimental:

*N,N'*Bis[*tert*-butyloxy]carbonyl]cystine dibenzyl ester:

13.04 g (29.5 mmol) *N,N'*-bis[(*tert*-butyloxy)carbonyl]cystine was dissolved in 170 ml of saturated sodium bicarbonate solution. During 30 min a mixture of benzyltriethylammonium chloride (13.49 g, 59 mmol) and benzyl bromide (12.10 g, 70.8 mmol) in 105 ml dried dichloromethane was added dropwise at $T=0^\circ\text{C}$. Then the mixture was stirred vigorously at room temperature for 6 days. The mixture was diluted with 120 ml water, washed with dichloromethane (2x20 ml), washed with saturated sodium chloride (50 ml) and dried over sodium sulphate. After removing of the solvent in vacuo, the yellow-white solid was recrystallized with chloroform/hexane (1:1) to yield 16.67 g of a white solid (91 % yield).

Analytics: FD-MS, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$

N-tert-butyloxycarbonyl cysteine benzyl ester:

8.20 g (13.2 mmol) *N,N'*-bis[(*tert*-butyloxy) carbonyl]cystine dibenzyl ester, 3.68 g triphenylphospine (14.0 mmol) and 430 mg (5 mmol) sodium acetate were suspended in 50 ml methanol, 26.5 ml water and 463 μl glacial acetic acid.

After heating to reflux the mixture was vigorously stirred for 24 h. The mixture was diluted with 150 ml of dichloromethane, washed with 120 ml of water and 150 ml of saturated sodium chloride solution and back-washed with 20 ml of dichloromethane. The organic phase was then dried over sodium sulphate and the solvent removed in vacuo, yielding 11.32 g of a clear yellow oil. Purification of the product via a solid phase extraction column (h: 80 cm, diethylether/hexane: 1:3, silica gel) and lyophilisation yielded 5.1 g of a white solid (64.8 % yield).

Analytics: FD-MS, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$

S-1,3-dimercaptopropylarsen-N-tert-butyloxycarbonyl cysteine benzyl ester:

100 mg (32 mmol) 1,3-dimercaptopropylarsenic iodide were synthesized according to [2] and without further purification 95 mg (32 mmol) of *N-tert*-butyloxycarbonyl cysteine benzyl ester and 25 μl pyridine (32 mmol) were added at $T=0^\circ\text{C}$. The mixture was allowed to stir for 30

min at room temperature and was then washed with water to give a pale yellow liquid after filtration.

Analytics: FD-MS of fractions before and after washing with water.

Results and Discussion: *N-tert*-butyloxycarbonyl cysteine benzyl ester was synthesized according to [3] with only slight modifications in the purification (silica gel column). In [2], the synthesis and stability of dimercaptoarsenic-precursors is described and so 1,3-dimercapto-propylarsenic iodide was chosen as an optimum for coupling to cysteine. The reaction scheme is shown in Fig.1.

The FD-MS spectra show that *S-1,3-dimercapto-propylarsen-N-tert*-butyloxycarbonyl cysteine benzyl ester can be purified by washing with water. The water-stability is important for future labelling in aqueous phases.

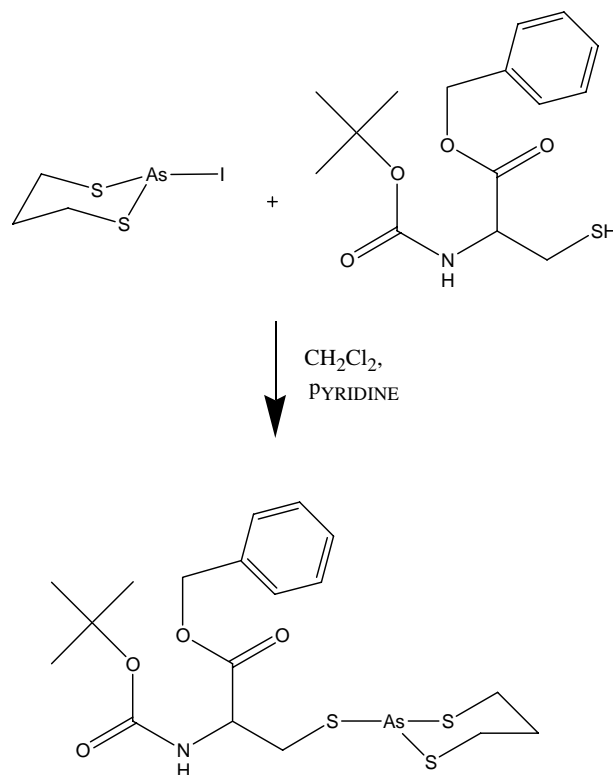


Fig. 1.: Reaction scheme of the synthesis of *S-1,3-dimercaptopropylarsen-N-tert*-butyloxycarbonyl cysteine benzyl ester

Conclusion: For the first time, an arseno-cysteine derivative could be synthesized and characterized via FD-MS. It represents an intermediate standard for future labelling of the amino acid cysteine with radioactive arsenic isotopes.

References:

- [1] Jennewein, M. et al., Annual Report 2002
- [2] Jennewein, M. et al., Annual Report 2003
- [3] Trost, B.M. et al., J. Org. Chem., 53 (1988)