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TETRAHEDRON: *ASYMMETRY*

Photochemical desulfurization of thiols and disulfides †

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Abstract

A visible light-induced desulfurization process for thiols and disulfides using triethylphosphite and triethylborane is reported. The reaction can be effected on a range of organic molecules having either primary, secondary or tertiary thiol groups and disulfides without the need of protecting groups. Thus, after treating L-cystine **7**, L-cystine dimethylester **8**, thioctic amide **9** and glutathione disulfide **10**, first with tributylphosphine, later with triethylborane/triethylphosphite under irradiation in a one-pot reaction, the corresponding desulfurized compounds L-Ala, L-Ala, 1-octanamide and γ-L-Glu-L-Ala-Gly, respectively, are prepared in high yields with retention of configuration.

1. Introduction

Reactions promoted by visible light are advantageous in many ways because of mild reaction conditions, cleaner reaction products and energy savings. Several reactions of synthetic importance have been satisfactorily performed under visible light irradiation.[1] We have recently accomplished the reductive desulfurization of L-cysteine derivatives, and an L-cysteine containing peptide, but no attempts were made to investigate other structural possibilities of the substrates.[2]

To broaden the scope of the reaction, we have first studied some aliphatic primary, secondary and tertiary thiol-containing organic molecules. Second, with the aim of developing new mild chemical tools for the study of the role of disulfide bridges in stabilizing and maintaining the biologically active conformations of complex peptides and proteins we have extended this photochemical desulfurization method to L-cystine and glutathione disulfide, simple models of such macromolecules.

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† Dedicated with affection to Professor Albert H. Soloway in his retirement.

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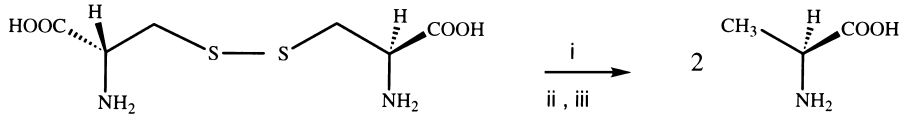
2. Results and discussion

A series of commercially available primary, secondary and tertiary thiols have been tested for desulfurization in the presence of triethylphosphite and triethylborane under light irradiation (see Table 1). The primary thiol group of captopril **1**, inhibitor of angiotensin converting enzymes, was removed in good yield (83%). However, a lower yield was obtained with 3-mercapto-1,2-propanediol **2** (47%). In the latter, side reactions of triethylboron with the hydroxyl groups of the substrate could give diethylborane ethers[3] or boron chelates,[4] competing with the reductive elimination of the thiol. Moderate yields were obtained for the removal of secondary thiol groups, for *N*-(mercaptopropionyl)glycine **3** (71%), and mercaptosuccinic acid **4** (65%). In addition, the tertiary thiol group of 8-mercaptomenthone **6** was eliminated in a satisfactory 78% yield, although lower than that observed with D-penicillamine **5** (95%).[2]

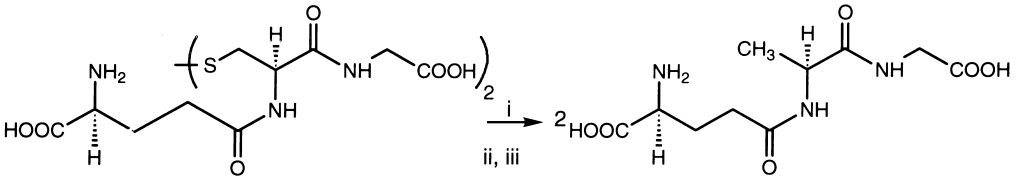
Initial attempts to remove the disulfide function of L-cystine under the same conditions failed. Due to the polar character of this substance the procedure had to be adapted to conditions using aqueous solvent. Previous reduction of L-cystine **7** with tributylphosphine in 1-propanol/water at room temperature according to Rüegg and Rudinger's procedure,[5] followed by light irradiation in the presence of triethylborane/triethylphosphite in a one-pot reaction, afforded L-alanine (90%) with retention of configuration (Scheme 1).



7

Scheme 1. Reagents: (i) $PBu_3/CH_3CH_2CH_2OH/NaHCO_3/H_2O$; (ii) BEt_3; (iii) $P(EtO)_3/h\nu$

In an analogous way, L-cystine dimethylester **8** furnished the desulfurized compound with concomitant hydrolysis of the ester under the mild basic reaction conditions (88%), and thioctic amide **9** afforded 1-octanamide in 86% yield. A blank reaction in the presence of triethylborane/tributylphosphine, but in the absence of triethylphosphite, showed only partial conversion of L-cystine to L-alanine (33%), tributylphosphine acting as a reducing and desulfurizing agent. Remarkably, the above reaction conditions were successfully applied to glutathione disulfide **10**, which was converted to the tripeptide, γ-L-Glu-L-Ala-Gly in 85% yield (Scheme 2).[6]

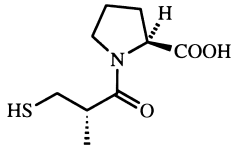
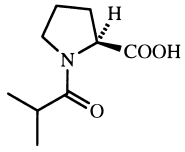
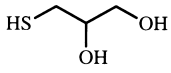
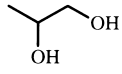
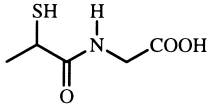
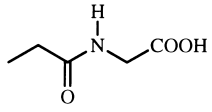
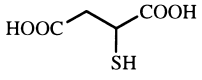
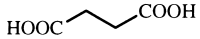
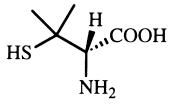
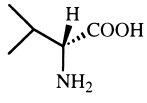
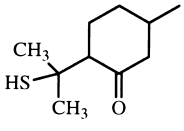
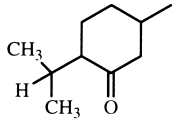
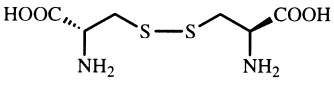
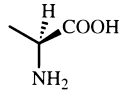
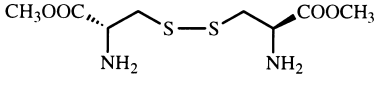
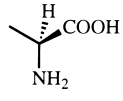
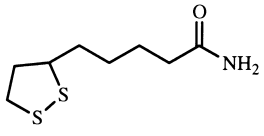
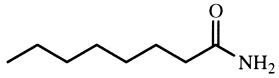


10

Scheme 2. Reagents: (i) $PBu_3/CH_3CH_2CH_2OH/NaHCO_3/H_2O$; (ii) BEt_3; (iii) $P(EtO)_3/h\nu$

In conclusion, we have demonstrated that this visible light induced desulfurization of thiols can be effected on a number of organic substrates regardless of their substitution pattern, effected by the combination of triethylphosphite and triethylborane. Moreover, reductive elimination of sulfur from disulfides is also possible using tributylphosphine as a previous reducing agent of the disulfide, even in the presence of water in a one-pot process. Studies aimed at the application of this process in peptide chemistry are currently underway in our laboratories.

Table 1
Desulfurization with triethylboron/triethylphosphite/hv[7]

Entry	Substrate[a]	Product	Yield (%)[b]
1			83
2			47
3			71[c]
4			65[c]
5			95[d]
6			78
7			90
8			88
9			86

[a] The reaction was carried out in CH_3CN with thiols **1** to **6** and in 1-propanol / 10%$NaHCO_3$/ H_2O with disulfides **7** to **9** for 36 h. [b] Yields of isolated compounds. All the products gave satisfactory NMR spectra compared with authentic samples.[c] Starting thiol was recovered (aprox. 25%).[d] Taken from ref.2.

Acknowledgements

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7. Typical experiment: L-cystine **7** (0.6 g, 2.5 mmol) was treated with 4 ml of 10% $NaHCO_3$, 6 ml of water and 10 ml of 1-propanol followed by 1.3 ml (5 mmol) of tributylphosphine under an argon atmosphere for 1 h at room temperature. A 1 M solution of triethylborane in tetrahydrofuran (3.5 ml, 3.5 mmol) was added and stirred under argon for 3 min. Triethylphosphite (2.6 ml, 15 mmol) was added and the resulting mixture was irradiated with a 300 W visible light bulb located about 20 cm from the flask for 36 h in an open system (Dimroth refrigerant). The solution became transparent. The organic solvent was evaporated under reduced pressure. 6 M HCl (6 ml) was added, the mixture stirred for 1 h and extracted with CH_2Cl_2 (3×2 ml). After evaporation of the acidic fraction under high vacuum, the residue was column chromatographed on silylated silica gel [Evans, M. B.; Dale, A. D.; Little, C. J. *Chromatographia* **1980**, *13*, 5–10] to give L-alanine hydrochloride (0.56 g, 90% yield). Selected spectral data: ^{13}C NMR (D_2O, 50 MHz) δ 175.0 (C=O), 51.2 (CH), 17.8 (CH_3). L-Ala·HCl: $[\alpha]_D^{22}$=+14.3 (*c* 10, 6N HCl), lit.: $[\alpha]_D^{20}$=+14.5 (*c* 10, 6N HCl). Glutathione disulfide **10** treated with tributylphosphine in 1-propanol/0.5 M $NaHCO_3$/water for 1 h followed by triethylborane for 2 min and irradiated in the presence of triethylphosphite for 14 h was converted into γ-L-Glu-L-Ala-Gly. The reaction was checked by RP-HPLC and MALDI-TOF-MS, [M+H]=276.10. ^{13}C NMR (D_2O, 50 MHz) δ 177.2, 175.5, 173.6, 172.0, 53.9 (CH), 51.5 (CH), 42.8 (CH_2), 32.6 (CH_2), 27.2 (CH_2), 18.6 (CH_3). Captopril **1** was converted into 1-(1-oxo-2-methylpropyl)-L-proline: ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.8, 173.1, 59.9 (CH), 47.5 (CH_2), 32.5 (CH), 27.6 (CH_2), 24.9 (CH_2), 19.0 (CH_3), 18.6 (CH_3). $[\alpha]_D^{20}$=−121 (*c* 1, ethyl acetate). M.p. 117–119°C.